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The Secretary of Health, Education, and Welfare has determined that the publication of this periodical is necessary in the transaction of the public business required by law of this Department. Use of funds for printing this periodical has been approved by the Director of the Office of Management and Budget through January 31, 1980.

Intensive Induction Therapy for Small Cell Carcinoma of the Lung [1,2]

Martin D. Abeloff,* David S. Ettinger, Nagi F. Khouri, and Raymond E. Lenhard, Jr [3,4]

SUMMARY

Fifteen patients with extensive small cell carcinoma of the lung and no prior therapy were treated with a chemotherapeutic regimen similar in intensity to the approach used in acute myelocytic leukemia. The patients received intensive induction therapy with cyclophosphamide, adriamycin, and VP-16-213 followed by treatment with a combination of BCNU, vincristine, methotrexate, and procarbazine. The objective response rate was 87% (13 of 15 patients) with three complete responses and ten partial responses. With the exception of one patient, the maximal response to therapy was achieved during therapy with the intensive cyclophosphamide, adriamycin, and VP-16-213 regimen. The three complete responders remain in remission for 159, 351, and 285 days but seven of the ten partial responders have relapsed and five of these have died. There was no unexpected morbidity associated with the intensive chemotherapy despite marked bone marrow suppression. This study demonstrates that very intensive combination chemotherapy can be safely used to achieve a high objective response rate in patients with extensive small cell carcinoma, but the complete response rate is low. An analysis of treatment failures and future directions is presented.

[Cancer Treat Rep 63:519–524, 1979]

Recent advances in the treatment of small cell carcinoma of the lung (SCC) with combination chemotherapy have resulted in an increase in objective response rates and prolongation of survival for patients with this type of lung cancer (1,2). However, the treatment of the extensive stage of SCC still poses a major challenge in that the complete response (CR) rate is generally $< 50\%$ and the median survival is only 10 months for patients with advanced SCC (2).

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[2]Supported in part by Public Health Service grant CA-06973 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

[3]The Johns Hopkins Comprehensive Cancer Center and the Department of Radiology, The Johns Hopkins Hospital, Baltimore, Md.

[4]We gratefully acknowledge the collaboration of The Johns Hopkins Comprehensive Cancer Center Clinical Information Systems and the technical assistance of Jo Jennings in the collection, calculation, and tabulation of the data presented in this paper. The excellent secretarial assistance of Nancy B. Kramer is also acknowledged.

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It has been suggested that an intensive chemotherapeutic approach similar to that used in acute myelocytic leukemia could result in an increased CR rate in SCC (3). Cohen et al (4) have reported that intensive chemotherapy with cyclophosphamide, CCNU, and methotrexate (CCM) is more effective than a lower dose regimen with the same drugs in SCC. We have previously shown that high-dose cyclophosphamide (60 mg/kg iv given either on Days 1 and 2 or on Days 1 and 8) can be safely administered to patients with SCC and results in a response rate of 70% (50% response rate in patients with extensive disease) (5). Based on these data regarding the efficacy and safety of high-dose chemotherapy in SCC and the promising results reported by Aisner et al (6) with a regimen of cyclophosphamide, adriamycin, and VP-16-213 (CAV), we designed a protocol to evaluate the effectiveness of very intensive induction therapy with CAV followed by treatment with a non-cross-resistant combination of BCNU, vincristine, methotrexate, and procarbazine (BOMP). This paper will describe the response rate and toxicity of this intensive chemotherapeutic approach in 15 patients with extensive SCC.

MATERIALS AND METHODS

Patient Selection and Therapy

Fifteen previously untreated patients with the extensive stage of SCC were entered in this protocol at The Johns Hopkins Oncology Center between May 1977 and June 1978. The diagnosis of SCC was established on the basis of bronchoscopic, lymph node, or liver biopsy. The diagnostic workup included a thorough history and physical examination, hemogram, electrolytes, glucose, BUN, creatinine, calcium, phosphorus, liver function studies, chest roentgenogram including tomograms and oblique views when indicated, bone marrow aspiration and biopsy, and bone and liver-spleen scans. Following this evaluation, patients were classified as having limited or extensive disease. *Limited disease* was defined as disease confined to one hemithorax including ipsilateral hilar and mediastinal nodes. *Extensive disease* was defined as disease beyond the hemithorax; patients with ipsilateral supraclavicular nodes, heterolateral mediastinal or hilar nodes, and pleural effusion (regardless of cytologic findings) were classified as extensive stage. Patients with central nervous system metastases at the time of diagnosis were not included in this study.

Patients with extensive SCC were treated with the protocol shown in figure 1. The therapeutic protocol consisted of two courses of CAV (cyclophosphamide, 2400 mg/m² iv; adriamycin, 60 mg/m² iv on Day 1; and VP-16-213, 125 mg/m² iv on Days 1, 3, and 5) administered at 28-day intervals while the patients were in the hospital. On Day 56, the patients started receiving BOMP on an outpatient basis (BCNU, 60 mg/m² iv; vincristine, 1.4 mg/m² [maximum, 2.0 mg] iv; methotrexate, 30 mg/m² iv on Day 56; and procarbazine, 100 mg/m²/day orally from Day 56 to Day 65). The vincristine and methotrexate were repeated on Day 70 and a second course of BOMP was started on Day 84. On Day 112 of the study, the patient's response status was reassessed. The complete and partial responders were scheduled for prophylactic cranial radiotherapy; they then received an outpatient modification of CAV (fig 1) alternating at monthly intervals with BOMP until progression. Nonresponders and progressors received individualized therapy.

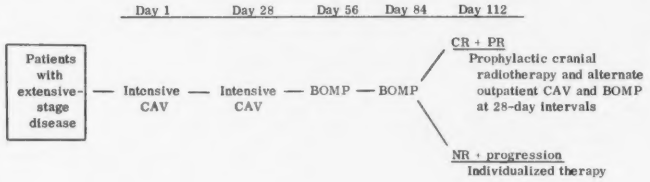
Assessment of response was made 4 weeks after each course of chemotherapy. *CR* was defined as the complete disappearance of all measurable lesions. *Partial response (PR)* was defined as a decrease of ≥ 50% in the product of the two longest perpendicular diameters of measurable lesions. *No response (NR)* was defined as a decrease of < 50% or an increase of < 25% over the original measurements of the product of the two largest perpendicular diameters of measurable lesions. *Progression* was defined as an increase of ≥ 25% over the original measurements of the product of the two largest perpendicular diameters of measurable lesions and/or the occurrence of new lesions. Duration of response and survival were calculated from the first day of chemotherapy.

RESULTS

Therapeutic Response

The clinical characteristics and response data of the 15 patients (nine males and six females) in this study are shown in table 1. The median age was 58 years (range, 46–65). All patients were evaluable. Determination of the Eastern Cooperative Oncology Group performance status (PS) at the initiation of therapy revealed that seven patients were symptomatic but ambulatory (PS 1), one patient was in bed for < 50% of the time (PS 2), three patients were in bed for > 50% of the time (PS 3), and four patients were bedridden 100% of the time (PS 4). The sites of metastases at the time of diagnosis are described in table 2. Three patients in this series presented with the superior vena cava syndrome.

The assessment of response status on Day 112 (following two courses of CAV and two courses of BOMP) revealed three CRs (20%), ten PRs (67%),



Intensive CAV
Cyclophosphamide: 2400 mg/m² iv x 1
Adriamycin: 60 mg/m² iv x 1
VP-16-213: 125 mg/m² iv, Days 1, 3, 5

BOMP
BCNU: 60 mg/m² iv x 1
Vincristine: 1.4 mg/m² iv, Days 1, 15
Methotrexate: 30 mg/m² iv, Days 1, 15
Procarbazine: 100 mg/m² orally, qd Days 1–10

Outpatient CAV
Cyclophosphamide: 1000 mg/m² iv x 1
Adriamycin*: 40 mg/m² iv x 1
VP-16-213: 100 mg/m² iv, Days 1, 3, 5

* Adriamycin will be discontinued at a total dose of 400 mg/m². The cyclophosphamide dose will then be increased to 1200 mg/m².

FIGURE 1.—Schedule of chemotherapy.

and two NRs (13%). With the exception of one patient (No. 2) who had tumor regression during BOMP therapy, the maximal response to therapy was achieved during the first 56 days of therapy and prior to the initiation of BOMP. There does not appear to be any correlation between response to therapy and initial PS or number of metastatic sites.

The three patients with CR remain in remission at 159, 351, and 285 days respectively. Seven of the ten partial responders have relapsed and five of these have died. The median duration of PR is 198 days with a range of 131 to +501 days. The median duration of survival of the partial responders is 243 days while the two nonresponders have survived +125 and 213 days respectively.

TABLE 1.—Clinical characteristics and response data for 15 patients treated with intensive induction therapy for SCC

Patient No.	Age in yrs/ sex	Eastern Cooperative Oncology Group PS	Initial sites of metastases	No. of metastatic sites	Response on Day 112	Duration of response (days)	Sites of progression	Duration of survival (days)	Comments
1	56/M	1	Bone, pleura	2	CR	+159	—	+159	
2	63/F	4	Ipsilateral supraclavicular nodes, marrow, heterolateral chest nodes, liver	4	CR	+351	—	+351	Response to BOMP
3	59/M	1	Heterolateral lung	1	CR	+285	—	+285	
4	59/M	3	Ipsilateral supraclavicular nodes, bone, marrow, liver	4	PR	+197	—	+197	
5	51/M	2	Ipsilateral supraclavicular nodes, bone, marrow, pleura	4	PR	131	Primary tumor, bone, marrow	+204	Presented with superior vena cava syndrome
6	51/M	3	Marrow, heterolateral chest nodes, liver, choroid	4	PR	199	Primary tumor, marrow, liver	322	
7	65/F	3	Liver	1	PR	155	Primary tumor, liver	227	
8	62/F	4	Bone, heterolateral chest nodes, liver, cervical nodes, pancreas	5	PR	159	Liver, abdominal nodes, peritoneum	176	Presented with superior vena cava syndrome
9	48/F	4	Bone, marrow, pleura, heterolateral chest nodes, liver	5	PR	227	Primary tumor, bone, liver, supraclavicular nodes	288	
10	53/M	1	Pleura, heterolateral chest nodes	2	PR	+259	—	+259	Presented with early superior vena cava syndrome
11	64/F	1	Marrow	1	PR	+501	—	+501	
12	65/M	1	Ipsilateral supraclavicular nodes	1	PR	298	Primary tumor	+351	
13	48/F	4	Bone, marrow, pleura, heterolateral chest nodes, cervical nodes	5	PR	131	Primary tumor, bone, marrow	222	
14	46/M	1	Heterolateral chest nodes	1	NR	—	Primary tumor	+125	
15	58/M	1	Heterolateral chest nodes	1	NR	—	Primary tumor, liver	213	

TABLE 2.—Sites of metastases at time of diagnosis

Site	No. of patients (%)
Heterolateral chest node	8 (53)
Marrow	7 (47)
Liver	7 (47)
Bone	6 (40)
Pleura	5 (33)
Ipsilateral supraclavicular nodes	4 (27)
Cervical nodes	2 (13)
Heterolateral lung	1 (7)
Pancreas	1 (7)
Choroid	1 (7)

Evaluation of the partial responders at Day 112 for sites of residual disease revealed that four patients had primary tumor as the only remaining evidence of measurable disease (table 3). Four patients had residual tumor at the primary site and in extrathoracic sites and two patients had residual disease only in extrathoracic sites. However, it is important to note that at the time when progression of tumor was noted in the seven partial responders, the primary tumor was the sole site of progression in only one patient (tables 1 and 4). Six patients had progression in the primary tumor and other extrathoracic sites, but none of these had significant clinical problems related to their progressive primary tumor. Evidence of relapse or progression was generally found at the sites of initial involvement. In patients 8, 9, and 15, relapse was also detected in new sites, ie, abdominal nodes and peritoneum, supraclavicular nodes, and liver respectively.

Toxicity and Supportive Care

All patients were hospitalized for the first two courses of intensive CAV therapy. The patients were treated in private rooms at The Johns Hopkins Oncology Center. The air system in these rooms is a Hepa-filtered air-flow system with 28 air changes/hour. Laminar air flow rooms or "life islands" were not used. Most patients could be discharged 24–36 hours after the initiation of chemotherapy and were re-admitted on Day 6 for the expected leukopenia. Prophylactic nonabsorbable oral antibiotics were not used in this study.

TABLE 3.—Sites of residual detectable disease in 10 partial responders

Site	No. of patients
Primary tumor only	4
Primary tumor + other sites	4
Liver	4
Bone	2
Bone marrow	1

TABLE 4.—Sites of progression in 7 partial responders

Site	No. of patients
Primary tumor only	1
Primary tumor + other sites	6
Liver	5
Bone	3
Bone marrow	3
Abdominal nodes	1
Peritoneal implants	1
Supraclavicular nodes	1
Central nervous system	0

In 30 courses of intensive CAV there were seven in which there was mild mucositis which did not limit normal oral intake, seven in which there was impairment of oral intake due to mucositis, and one in which the mucositis transiently prevented any oral intake. Most patients experienced a moderate degree of nausea and vomiting on the day of CAV administration. Alopecia occurred in all patients. No cases of hemorrhagic cystitis occurred in this series. Two patients developed severe peripheral neuropathy during the first two courses of CAV prior to the initiation of the vincristine-containing BOMP regimen. Because a thorough neurologic evaluation did not reveal the etiology, a drug-induced neuropathy was considered a likely possibility.

The intensity of the CAV induction regimen is reflected in the hematologic toxicity. The curves of the mean wbc and platelet counts during the first course of intensive therapy with CAV in 15 patients are shown in figure 2. These curves are essentially

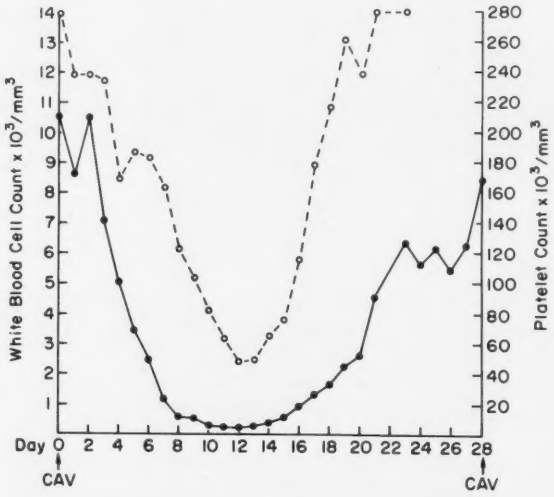


FIGURE 2.—Curves of mean wbc (•—•) and platelet (o--o) counts during 1st course of intensive CAV therapy.

identical for the second course of CAV therapy. During the first and second courses of intensive CAV the median wbc count nadirs were 121 and 143/mm³ respectively and the median platelet count nadirs were 41,000 and 23,000/mm³ respectively. During a course of intensive CAV, the wbc count was < 1000/mm³ for an average of 8 days while the platelet count was < 50,000/mm³ for an average of 4 days.

There were 26 febrile episodes in the 30 courses of CAV. Sites of infection and/or positive cultures were noted in 45% of febrile episodes, but patients were routinely treated with carbenicillin and gentamicin or carbenicillin and co-trimoxazole (Bactrim) when a temperature of > 38.3°C occurred along with a granulocyte count of < 1000/mm³. Antibiotics were discontinued when patients became afebrile and the granulocyte count was > 1000/mm³. Patients were treated with antibiotic therapy for an average of 6 days during each course of intensive CAV therapy. Leukocyte transfusions were not used in this study.

Platelet transfusions were administered to patients with platelet counts of < 20,000/mm³ and were used in 11 of 30 courses of intensive CAV. There was one episode of a bleeding complication related to thrombocytopenia. Patient 3 had a history of peptic ulcer disease and developed transient gastrointestinal bleeding during CAV therapy. Rbc transfusions were given in eight of 30 CAV courses. No deaths occurred as a complication of the intensive induction therapy.

After receiving the two courses of CAV while in the hospital, the patients received two courses of BOMP as outpatients (fig 1). Complete and partial responders then received prophylactic cranial radiotherapy and an outpatient modification of CAV alternating at monthly intervals with BOMP. During 86 courses of outpatient therapy, there were eight episodes of wbc counts of < 1000/mm³ and ten episodes of platelet counts of < 50,000/mm³. Five of the 86 courses of treatment resulted in hospitalization for management of fever and leukopenia.

Alteration of drug doses was made on the basis of hematologic toxicity in only one patient during the first two courses of therapy. Three additional patients had dose modifications during the two courses of intensive CAV because of associated medical problems (eg, cardiac arrhythmias). The mean percentages of planned doses of each drug administered during the first six courses of therapy are shown in table 5.

TABLE 5.—Mean % of planned doses administered per course

	Course					
	1	2	3	4	5	6
Cyclophosphamide	98	88			75	
Adriamycin	88	90			60	
VP-16-213	100	100			60	
BCNU			99	85		81
Vincristine			77	89		74
Methotrexate			74	80		77
Procarbazine			73	60		71

DISCUSSION

Although the overall objective response rate to intensive induction chemotherapy in this study was 87%, the CR rate was only 20%. Within 2 months of the initiation of high-dose therapy with CAV, the responding patients had a marked reduction in tumor size with a significant improvement in PS. However, residual tumor was detected in ten of the 13 responding patients, generally at the site of initial involvement. Seven of the ten partial responders have relapsed and five of these have died. With the exception of one patient, no further objective regression of tumor was seen during treatment with BOMP and subsequent therapy with an outpatient modification of CAV.

This study was designed to evaluate the effectiveness of very intensive induction chemotherapy (two courses of CAV) followed by a non-cross-resistant combination (BOMP) in producing a high CR rate in SCC. Cohen et al (4) previously reported that high-dose chemotherapy results in greater response rates and longer survival than standard-dose chemotherapy. In a prospective randomized study these investigators compared standard-dose chemotherapy using CCM to a high-dose program using the same drugs. The overall response rate was 96% (30% CR rate) in 23 patients (including limited- and extensive-disease patients) receiving high-dose therapy, while the objective response rate was 45% (0 CR rate) in patients receiving standard-dose chemotherapy. The CAV regimen used in our study was more intensive and resulted in greater hematologic toxicity than Cohen's CCM program, but the increase in the intensity of our therapy did not result in an improvement in the CR rate. There was a difference in the patient population in these two studies in that patients with a PS of > 2 were excluded from the CCM protocol whereas seven of the 15 patients (47%) in our study had a PS of 3 or 4. Nevertheless, the fact remains that the brief, very intensive induction regimen with CAV resulted in a CR rate of only 20% (a 25% CR rate in patients with a PS of 1 or 2) in this group of patients with widely metastatic SCC.

In the CCM study, no patient who had a PR at the end of 6 weeks of therapy subsequently achieved a CR while receiving maintenance therapy with standard-dose CCM. In an attempt to increase the

CR rate, Cohen et al (7) subsequently designed a study in which patients received a non-cross-resistant chemotherapy regimen consisting of vincristine, adriamycin, and procarbazine following the initial 6-week treatment with CCM. The crossover to vincristine, adriamycin, and procarbazine resulted in an increase of the CR rate from 24% at 6 weeks to 40% at 12 weeks. However, in our study, only one of ten partial responders had a further objective response to our alternate BOMP regimen.

It is possible that our response rate might have been improved by administering the drugs at a shorter interval (< 28 days), by increasing the doses of individual agents or the number of intensive courses of chemotherapy, or by using a different sequence of the same drugs. However, the results in our study are consistent with those of other recent aggressive approaches to extensive SCC. Brereton et al (8) used a regimen of intensive cyclic chemotherapy (cyclophosphamide, vincristine, and adriamycin) administered concurrently with radiotherapy of bulk disease plus prophylactic whole-brain irradiation. Ten of 21 patients with extensive disease had a CR but the median survival time for these patients was only 10.5 months. Severe multiorgan toxicity including treatment-related deaths was noted in this study. Greco et al (2) have reported a pilot study of a combination of high-dose methotrexate with leucovorin rescue and cyclophosphamide, adriamycin, and vincristine in nine selected ambulatory patients with extensive SCC. Although seven of the nine patients were reported to have a CR, the mean duration of response was only 8 months and the median survival time was 11 months. In an assessment of long-term results of their multimodality approach with combination chemotherapy (cyclophosphamide, adriamycin, and vincristine), radiotherapy to the lung primary, prophylactic whole-brain irradiation, and bacillus Calmette-Guérin immunotherapy, Einhorn et al (9) reported a median survival time of only 36 weeks in 39 patients with extensive disease.

Thus, it appears that combination chemotherapy may have reached a plateau in its capacity to induce durable CRs for most of the patients with extensive SCC. Certainly, it has been well-documented in this study and other reports that intensive combination chemotherapy can be safely used in SCC. Intensive induction therapy and the use of alternating non-cross-resistant chemotherapy regimens deserve further exploration in controlled studies, but other innovative approaches must also be investigated. Sequencing of drugs based on cellular kinetics of the tumor and the normal hematopoietic cells in the marrow is being studied in a variety of malignancies including SCC (5,10). The use of intensive therapy after induction of CR (late intensification) has been advocated by Norton and Simon (11) who have presented clinical and mathematic data to support high-dose therapy when the tumor burden is low. In addition to developing new approaches to chemotherapy, the role of radiotherapy in extensive SCC should be re-assessed. In this study, relapse and progression generally occurred at the sites of initial involvement so that the use of radiation therapy to sites of bulk disease should be re-evaluated in future protocols. Half- or whole-body radiation therapy should also be studied as adjuncts to systemic chemotherapy in advanced SCC. The ability to combine intensive chemotherapy and radiotherapy in an optimal fashion may also be enhanced by the use of autologous marrow infusion in selected patients. Careful analyses of the reasons for treatment failures plus integration of the therapeutic techniques of medical and radiation oncology will hopefully result in significant improvements in the therapy for extensive SCC.

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Phase II Trial of Dianhydrogalactitol in Metastatic Malignant Melanoma: A Southwest Oncology Group Study [1,2]

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SUMMARY

Dianhydrogalactitol given iv in a schedule of 30 mg/m²/day for 5 consecutive days every 4 weeks was administered to 27 patients with metastatic malignant melanoma. All patients had received extensive prior therapy including chemotherapy and had progressive disease at the start of the study. Of 24 patients evaluable for response, 21 demonstrated progressive disease and three had stable disease for periods of from 4 to 11 months. No objective responses were observed. Two of the remaining three patients died 6 and 10 days after entry in the study, while the third refused to return after one drug course. Adverse effects included myelosuppression in eight patients, nausea and vomiting in five patients, and alopecia in one patient. Dianhydrogalactitol is considered to be insignificantly active in the secondary treatment of metastatic malignant melanoma at the dose and schedule studied.

[Cancer Treat Rep 63:525–528, 1979]

At least two dibromohexitols, dibromodulcitol and dibromomannitol, are known to exert cytostatic effects on tumor cells. When treated with mild alkali or human serum, these compounds are converted to the corresponding diepoxy derivative (1). The diepoxy derivative is thought to be responsible for the observed cytostatic action of its corresponding dibromohexitol (2,3); 1,2:5,6-dianhydrogalactitol (DAG) is the diepoxy derivative of DBD. DAG, like its parent compound, is thought to act as an alkylating agent (4,5) to inhibit DNA, RNA, and protein synthesis (6). DAG did, however, produce greater inhibition than its parent compound and thus was selected for further investigation (7). Preclinical trials revealed significant inhibition of tumor growth and prolongation of survival in five mouse and five rat tumors (8). The major adverse effect was depression of myeloid and lymphoid cells (8). Phase I trials were carried out using four dose schedules: single dose every 3 weeks (9), five consecutive daily doses every 4 weeks (10), ten consecutive daily doses (10), and weekly doses (11). The dose-limiting toxicity in these trials was myelosuppression, more often affecting platelets than leukocytes and more common and severe in patients who had received prior nitrosoureas. Responses included two patients with renal cell carcinoma, one with adenocarcinoma of the lung, and one with laryngeal carcinoma. Upon completion of these studies, the drug was used in phase II trials by the Southwest Oncology Group in patients with a variety of solid tumors. Among these trials was a study in patients with advanced malignant melanoma.

MATERIALS AND METHODS

At ten member institutions of the Southwest Oncology Group, 28 adult patients with biopsy-proven metastatic malignant melanoma were evaluated with regard to age, sex, race, history of prior treatment, performance status, site of primary disease, extent of metastatic disease, hematologic parameters, and liver and renal function. The median age of the patients was 51 years (range, 27–74 years). As would be expected in a population of

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TABLE 1.—Characteristics of patients studied

Characteristic	No. of patients
Prior treatment	28
Surgical resection	26
Radiation	7
Chemotherapy	28
Immunotherapy	16
Performance status	
80%–100%	4
50%–70%	19
< 50%	5

patients with malignant melanoma, 27 were white and one was black. Of the 28 patients, 16 were male and 12 were female. All patients had received extensive prior treatment (table 1). Six of the 28 patients had received two different drug regimens previously; in the remaining 22 DAG represented second-line therapy. Nineteen of the 28 patients had received BCNU as a part of their prior chemotherapy. According to initial performance status, most patients were symptomatic and partially bedridden. Twenty-four of the 28 had extensive metastatic disease as reflected by multiple sites of involvement (table 2). At the time of study entry all patients were required to have a leukocyte count of ≥ 4000/μl and a platelet count of ≥ 100,000/μl. No patient was entered until recovery from effects of prior treatment had occurred.

Twenty-seven of 28 patients received DAG. For those with normal tolerance to prior chemotherapy, no prior nitrosoureas, and normal renal and liver function, DAG was administered at a dose of 30 mg/m²/day iv for 5 days once every 28 days. Doses were reduced to 25 mg/m²/day for patients with poor tolerance to prior chemotherapy, prior nitrosoureas, or impaired hepatic function as reflected by a bilirubin level of > 2.0 mg/100 ml. For patients with impaired renal function (creatinine clearance < 65 ml/minute) or only one functioning kidney, doses were reduced to 15 mg/m²/day. Among the 28 patients studied, 19 received an initial dose of 25 mg/m²/day, eight received 30 mg/m²/day, and one died prior to receiving any therapy. In those patients with no evidence of either myelosuppression or progressive disease, doses in subsequent courses were escalated in 5-mg/m²/day increments. For excessive myelosuppression, doses were reduced. If the lowest recorded granulocyte count was < 1000/μl or if the lowest recorded platelet count was < 50,000/μl, doses were reduced by 5 mg/m²/day. A patient was considered to be evaluable for response if he received one course of drug and lived 4 weeks. A patient was considered to be evaluable for toxicity if he received one course of drug regardless of subsequent survival.

TABLE 2.—Primary and metastatic sites of disease

Sites	No. of patients
Primary site	
Trunk	6
Upper extremity	6
Lower extremity	6
Head and neck	3
Eye	4
Unknown	3
Site of metastasis	
Skin	16
Nodes	14
Lung	18
Bone	11
Liver	8
Brain	6
Eye	1
Thyroid	1
Multiple sites	24

Response was defined as follows: *complete response*—disappearance of all evidence of disease; *partial response*—a ≥ 50% reduction in the product of perpendicular diameters of each measurable lesion; *progressive disease*—a ≥ 50% increase in the product of perpendicular diameters of any measurable lesion or the appearance of any new lesion; and *stable disease*—a < 50% regression or progression of lesions. Response or disease stabilization was recorded only if the observed status persisted for ≥ 1 month.

RESULTS

Of the 28 patients entered in the study, one died prior to receiving any DAG. The remaining 27 patients received one or more courses of DAG. Of these 27 patients, three were inevaluable for response: two died 6 and 10 days respectively after initiation of therapy while the third refused to return after completing the first course of therapy. Among the remaining 24 patients evaluable for response, the median number of drug courses per patient was two (range, one to 11); 16 of the 24 received two or fewer drug courses. No complete or partial responses were observed. Twenty-one of the 24 patients were removed from the study because of progressive disease during therapy. Three patients demonstrated stable disease for periods of > 1 month, with the longest period of stabilization reaching 11 months in a patient with extensive metastatic disease to skin, nodes, and lung after two prior drug regimens.

All 27 patients who received the drug were considered to be evaluable for toxicity (table 3). Sixteen

TABLE 3.—Adverse effects

Effect	No. of patients
Myelosuppression	8
Leukopenia (cells/μl)	5
Nadir, 3000–4000	2
Nadir, 2000–3000	3
Median nadir, Day 28 (range, Days 15–53)	
Thrombocytopenia (cells/μl)	7
Nadir, 75,000–100,000	2
Nadir, 50,000–75,000	3
Nadir, 25,000–50,000	2
Median nadir, Day 28 (range, Days 19–42)	
Gastrointestinal (nausea and vomiting)	5
Mild	3
Moderate	2
Alopecia	1

patients experienced no observable adverse effects. Eight patients experienced significant myelosuppression. Five of these eight were noted to have leukopenia (wbc count < 4000/μl), with a median lowest recorded leukocyte count of 2900/μl (range, 2700–3500/μl) and a median time of occurrence of Day 28 (range, Days 15–53) after the start of drug administration. Four of these five developed their lowest leukocyte counts during course 1 or 2, while the remaining patient developed leukopenia after course 8. Seven of the eight patients were noted to have thrombocytopenia (platelet count < 100,000/μl), with a median lowest recorded platelet count of 60,000/μl (range, 25,000–90,000/μl) and a median time of occurrence of Day 28 (range, Days 19–42) after the start of drug administration. Of these seven patients, the lowest platelet count occurred after course 1 in three patients and after courses 2, 3, 5, and 6 in one patient each.

Other adverse effects reported included nausea and vomiting (mild in three patients and moderate in two) and alopecia (one patient only).

DISCUSSION

DAG was selected for phase II clinical trial because of a suggestion of activity in preclinical (8) and phase I clinical (9–11) trials. Interest in this particular drug also stemmed from unpublished data which suggested that it penetrates the cerebrospinal fluid in significant quantities and thus may be useful in the management of either primary or metastatic central nervous system neoplasms. The current study was undertaken to determine whether DAG would be a new active drug in the treatment of advanced malignant melanoma.

Results indicate that DAG has no significant efficacy in the treatment of malignant melanoma. Although three of 24 patients did demonstrate some evidence of disease stabilization, no objective regressions were observed. Although it is true that all patients had received extensive prior therapy and that 86% of the patients were at least symptomatic and partially bedridden, some evidence of activity should have been seen if the drug has any efficacy in the treatment of melanoma. That the dose and schedule tested represent an adequate drug trial is evidenced by the fact that myelosuppression of a significant degree was observed in eight of 27 patients (30%).

Adverse effects of DAG in this study were acceptable and were manifested almost exclusively as myelosuppression and gastrointestinal toxicity. There is no evidence in this patient population of any cumulative effect on bone marrow, but the fact that 16 of 27 patients received two or fewer drug courses renders any conclusion in this regard unwarranted. No drug-related deaths occurred.

In conclusion, DAG appears to be inactive in the treatment of advanced malignant melanoma at the dose and schedule tested.

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Experimental Skin Necrosis Produced by Adriamycin [1,2]

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SUMMARY

Skin ulceration caused by extravasation of Adriamycin follows a severely protracted course accompanied by considerable morbidity. To develop an animal model of Adriamycin ulceration, we compared intradermal injection of Adriamycin to injection beneath the panniculus carnosus with varying drug volumes and concentrations. Injections beneath the rat panniculus carnosus caused only irregular ulcerative lesions. Intradermal injection produced predictable, uniform skin necrosis and ulceration. Both increasing volume and increasing concentration of Adriamycin caused proportionate increases in skin ulcer size and in time required for healing. A critical concentration range for Adriamycin necrosis is 0.010–0.020 mg/ml, suggesting that the drug would have to be greatly diluted to reduce clinical skin ulceration. Adriamycin-induced skin necrosis heals at a slower rate than surgically created skin defects of similar size, indicating a reduced rate of wound contraction. Removal of the necrotic skin allows faster healing, although still slower than normal, due to removal of splinting effect. Histology shows early skin necrosis, with acute inflammation developing after 1 week. Epidermal hypertrophy is present at the edges of the necrosis. The small vessels remain patent. Multiple small vesicles of unknown etiology are seen in the necrotic dermis.

[Cancer Treat Rep 63:529–537, 1979]

Adriamycin has proven to be a potent chemotherapeutic agent for the treatment of a variety of hematologic and solid cancers (1,2). Although cardiotoxicity, gastrointestinal side effects, and myelosuppression from the use of Adriamycin have been well-recognized and investigated (1,2), chronic skin ulceration occurring after extravasation of the drug-bearing solution has been less well-studied. As noted by Rudolph et al (3,4), skin ulcers due to extravasated Adriamycin behave much like chronic radiation ulcers, with great morbidity and a prolonged clinical course.

Because of the severe morbidity of these ulcers, an animal model was needed to study both the etiology of these ulcers and their treatment. Studies by Adria Laboratories demonstrated irregular ulceration when the drug was given by standard pharmacologic testing methods, which involved grasping the animal skin and depositing the drug sc. Rodents have a panniculus carnosus, a thin muscle layer intimately adherent to the skin, and substances placed beneath the panniculus are not in direct contact with the skin. Further, the panniculus carries its own blood supply and nourishes the skin, as opposed to human skin which receives its circulation from vessels in the subcutaneous space.

Because of these anatomic differences, we theorized that to produce experimental ulcerations in rodents, Adriamycin would have to be delivered directly to the skin. This study was designed to compare methods of drug delivery to the skin and to develop a reproducible model.

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MATERIALS AND METHODS

Rats.—One hundred and twenty Sprague-Dawley rats (250–300 g) were divided into groups of five and were injected with Adriamycin in nonbacteriostatic saline or with lactose/saline solution. All animals were anesthetized ip with Nembutal, and two injections were given on the anterior and posterior dorsal skin of each animal. Intradermal injections were done using a No. 25 needle, ballooning the dermis with solution. Subpannicular injections were performed by picking up the loose dorsal skin and placing the solution below the panniculus carnosus. The skin was shaved with a hair clipper before injection.

Adriamycin injections were performed in two series: (*a*) constant concentration (2 mg/ml) with varying volumes (0.1–1.0 ml); and (*b*) constant volume (0.5 ml) with varying concentrations (0.002–2.000 mg/ml). Control injections, both intradermal and subpanniculus, were done with 0.5 ml of lactose (1.0% in normal saline).

To have a standard against which to measure the rate of closure of the skin lesions, skin was excised from two groups of five rats. In one group, a circle (15 mm in diameter of full-thickness skin and panniculus) was excised. In the second group, skin only (of a similar diameter) was excised, leaving the panniculus carnosus intact.

The animals were housed in a laminar air flow room to minimize the potential of cross-animal infection and were followed weekly with measurements of skin lesion size and body weight. At intervals of 1, 3, and 5 days and weekly thereafter, biopsies of the skin lesions were obtained for histologic examination.

After the development of skin necrosis, a group of ten animals had debridement of the necrotic eschar at 2 weeks. The remainder of the rats were allowed to separate the necrotic skin spontaneously. Measurement of lesion diameter in the animals with the eschar removed could be done directly. In the animals with the eschar in place, lesion size was measured by trimming the edges of the eschar to the point at which it became adherent to the underlying tissue, and measuring this diameter.

RESULTS

Ulcer Appearance and Measurements

Animals given either intradermal or subpanniculus injections with the control lactose/saline solution developed no ulceration or skin inflammation. Transient edema at the injection site disappeared within 1 day.

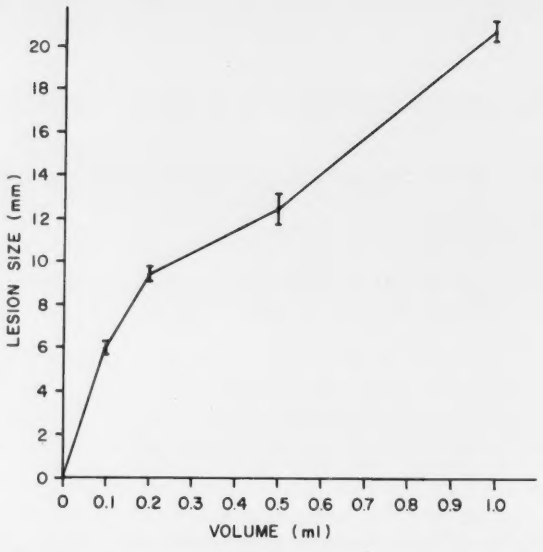

FIGURE 1.—Linear relationship of size of skin necrosis at 2 wks and increasing volumes of intradermal Adriamycin (2 mg/ml). Brackets = 1 SEM.

Adriamycin injected at a constant concentration of 2 mg/ml uniformly produced skin necrosis. The size of the lesions varied directly with the volume injected (fig 1) as did the length of time required for the ulceration to heal (fig 2). A dry eschar of necrotic dermis and epidermis developed in the area of injection. This eschar subsequently became undermined by epidermis followed by sloughing of the dead skin.

Animals given intradermal Adriamycin in a volume of 0.5 ml but with varying concentrations also demonstrated a constant relationship between the dose, the size of the lesion (fig 3), and the rate of healing (fig 4). The more concentrated the drug, the larger the initial skin lesion and the longer it took to obtain a closed wound. Since initial dermal spread was the same for all injections, lesion size was directly related only to drug concentrations. Only small lesions were produced at the initial low dilution of 0.002 mg/ml. Lesion size increased rapidly as concentrations rose to 0.020 mg/ml. After this concentration, there was a slower rise in lesion size, with only a 2-mm lesion size difference seen between 0.200 and 2.000 mg/ml. Thus, a critical concentration for development of Adriamycin necrosis in rat skin lies between approximately 0.010 and 0.020 mg/ml (fig 3).

Subpanniculus injections of Adriamycin at a constant concentration of 2 mg/ml produced irregular necrosis (fig 5). At volumes > 0.1 ml, lesions devel-

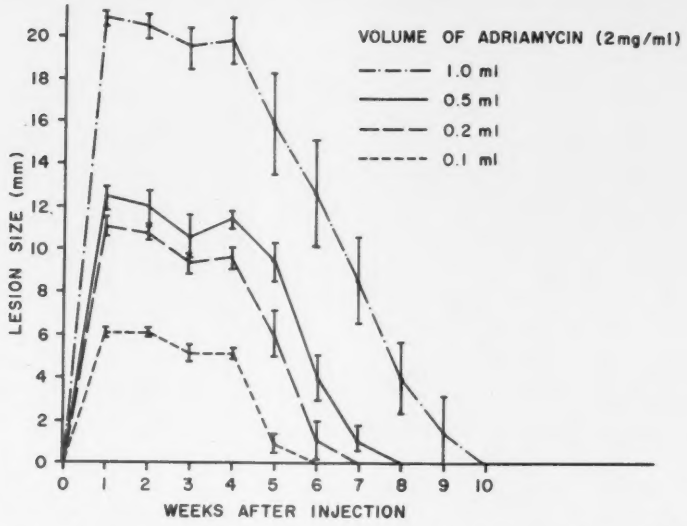

FIGURE 2.—Size of lesions and time needed for healing of skin necrosis caused by intradermal Adriamycin (2 mg/ml). Brackets = 1 SEM.

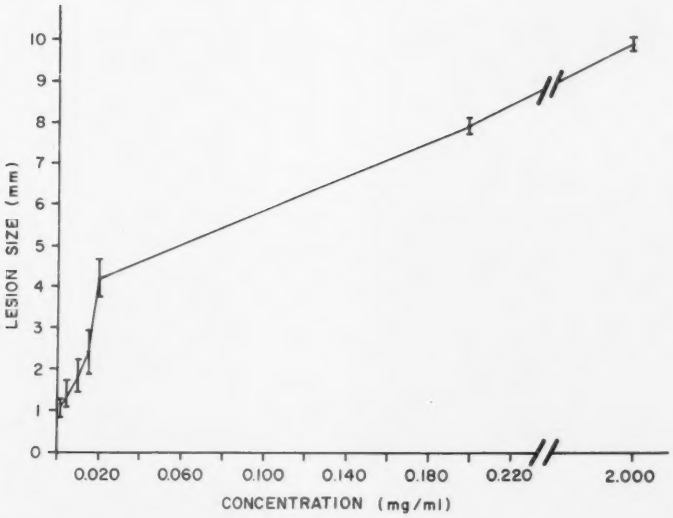

FIGURE 3.—Skin necrosis size at 2 wks after intradermal injection of increasing concentrations of Adriamycin (0.5 ml). Rapid increase in lesion size occurs at concentrations of 0.010–0.020 mg/ml. Brackets = 1 SEM. [Reprinted from *Orthopaedic Review* (ref 4).]

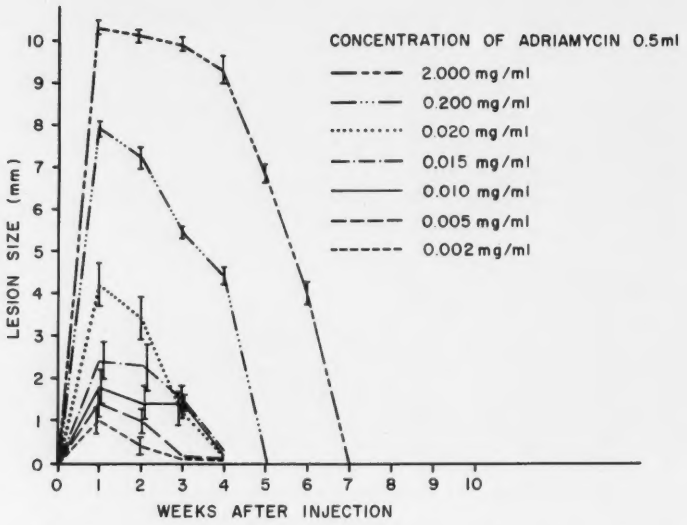

FIGURE 4.—Size of lesions and time needed for healing of skin necrosis caused by varying concentrations of intradermal Adriamycin. Brackets = 1 SEM.

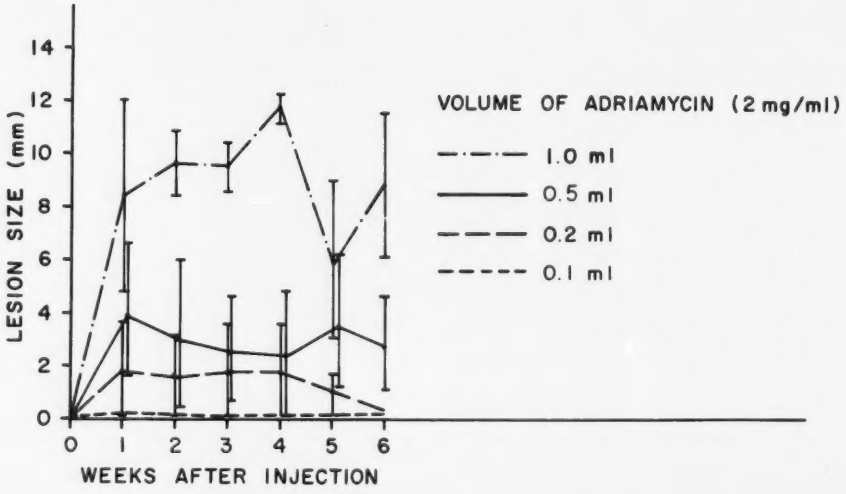

FIGURE 5.—Skin ulcer size produced by subpannicular injection of Adriamycin (2 mg/ml). Lesions were irregular and unpredictable as shown by large SEMs.

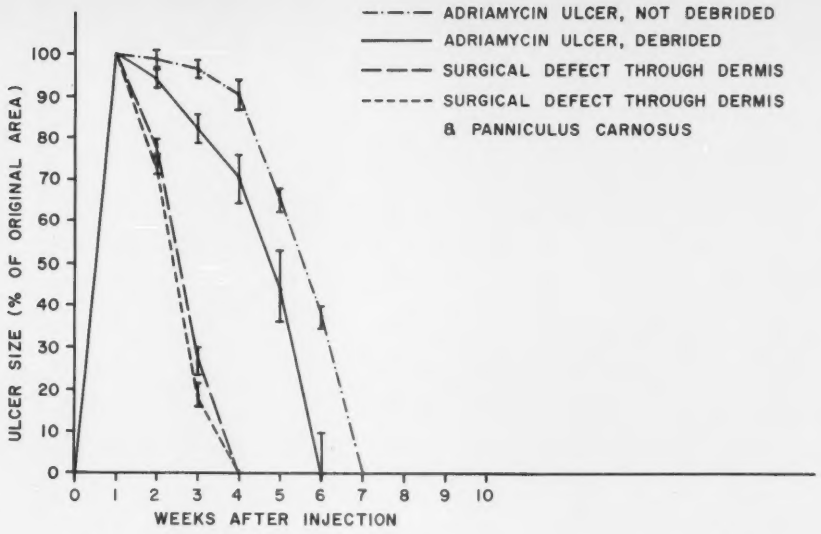

FIGURE 6.—Rate of healing of surgically created wounds compared to rate of healing of skin ulcers 1 wk after intradermal injection. More rapidly healing Adriamycin lesions had necrotic skin debrided 2 wks after injection. Brackets = 1 SEM.

oped that consisted mostly of clusters of small ulcers. Lesion size was larger when larger subpanniculus volumes were given (fig 5), but these lesions were irregular, making this an unsatisfactory model to study Adriamycin injury.

Figure 6 compares the healing of Adriamycin-induced lesions to the healing of defects surgically created. Skin loss created by a 15-mm diameter surgical excision of dermis, or of dermis with panniculus carnosus, led to closure of the wound within 3 weeks. Animals receiving intradermal injections of Adriamycin demonstrated slower closure of 12-mm ulcers, with 7 weeks needed for complete healing. Removal of the necrotic eschar speeded spontaneous closure of Adriamycin-induced lesions.

Histology

Controls.—No significant changes were seen other than transient edema within the dermis or in the subpannicular layer after injection.

Adriamycin injections.—On the first day after injection, edema of the dermis was seen, without an acute inflammatory response or necrosis. By the third day, necrosis of dermis and epidermis was evident (fig 7). The prominent findings consisted of coagulation of the dermis with pyknotic nuclei and darker staining of collagen. The epidermis appeared nonviable in the injection area. The vessels did not appear to be occluded, and there was a striking lack of acute inflammatory response. An unexplained early finding was small vesicles lying within the injected dermis. These appeared to be more prominent in straight lines, as though they followed the track of injection.

By 7 days (fig 8), necrosis of the skin occurred, with an inflammatory reaction as the lesion demarcated and sloughed. At 6 weeks, late ulcers or healed scars (fig 9) demonstrated chronic granulation tissue and fibrosis, with hypertrophy of the surrounding epidermis. Small vessels remained patent within the viable tissue at the edge of the eschar. As ulcers healed, histology continued to show dense connective tissue scarring and epidermal hyperplasia, which remained at least through 10 weeks after injection. Subpanniculus injections produced necrosis of the panniculus carnosus and loose fascia beneath the panniculus, with occasional areas of skin necrosis.

DISCUSSION

In extensive animal and human experience, Adriamycin is an effective chemotherapeutic agent for the treatment of solid tumors such as breast cancer, lymphoma, sarcoma, and thyroid cancer (1,2,5). Accidental extravasation of the drug leads to a very severe skin ulceration with extended morbidity (2–7), which may require extensive surgical correction (3,4,6). The clinically seen ulcers lack the ability to

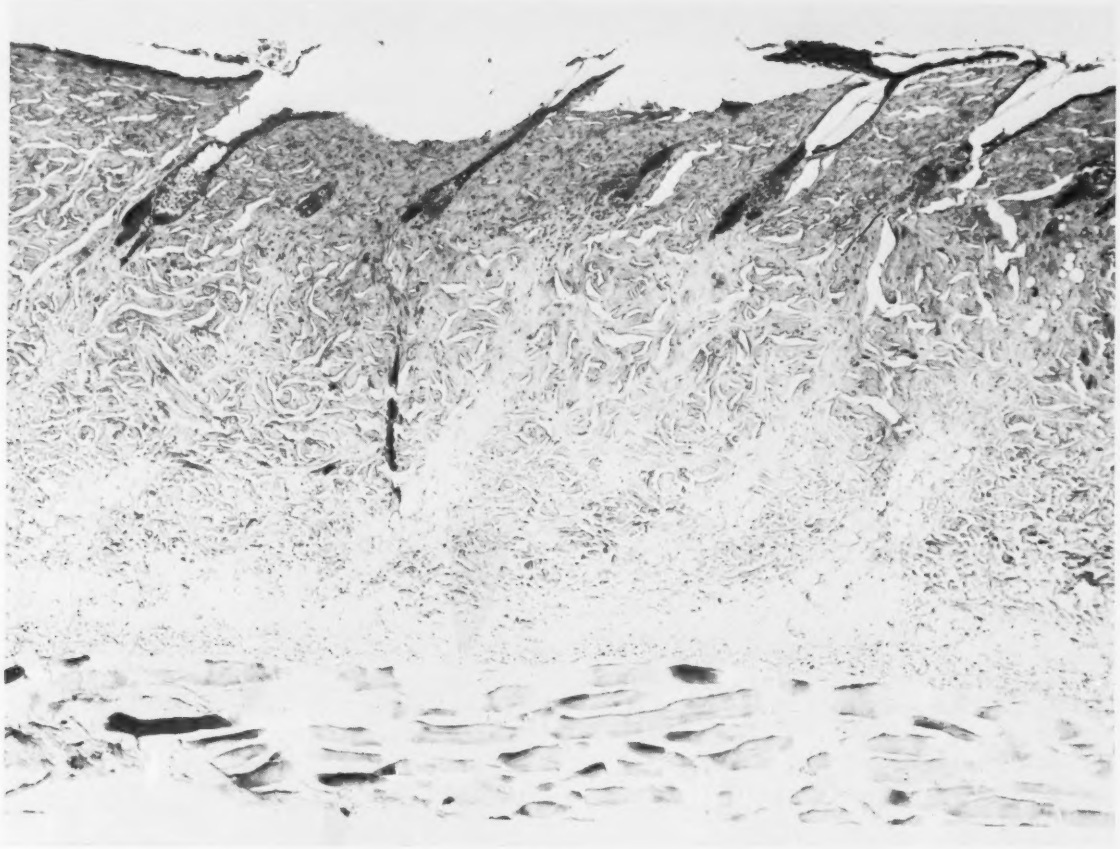

FIGURE 7.—Rat skin 3 days after intradermal injection of Adriamycin. Necrosis of dermis and epidermis with edema of muscle is shown. Small vesicles are present within the necrotic dermis. Hematoxylin and eosin, × 40.

FIGURE 8.—Rat skin 7 days after intradermal Adriamycin. Dermis is necrotic and epidermis has sloughed. Hematoxylin and eosin, × 40.

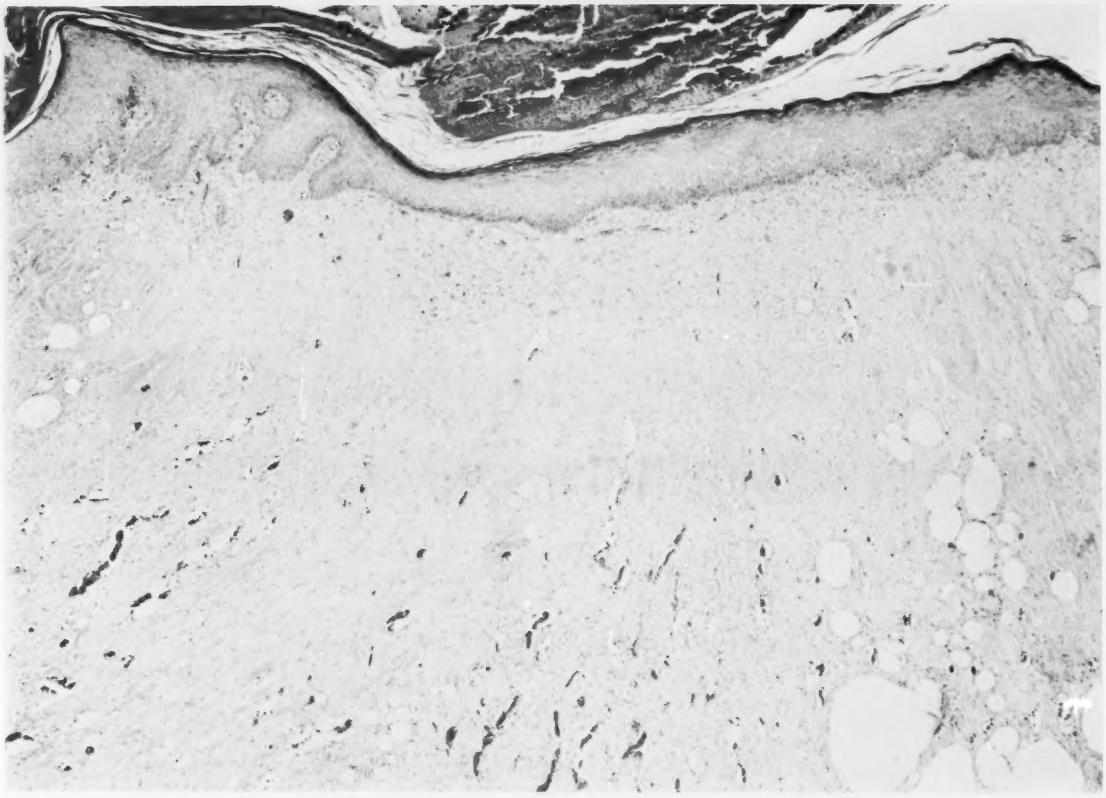

FIGURE 9.—Healed rat skin 6 wks after Adriamycin injection. Dense dermal scarring with epidermal hypertrophy is shown. New blood vessels and empty vesicles are prominent. Hematoxylin and eosin, × 40.

contract, or they contract at only a slow rate, and deep structures such as tendon and bone can become exposed and necrotic.

Grossly, skin ulcers caused by Adriamycin in man resemble radiation ulcers. They have shaggy, necrotic bases with rolled painful edges and a surrounding area of erythema (3,4). They do, however, lack the characteristic telangiectasia and atrophy of radiation-induced ulcers (8). Histologically, in man, ulceration due to Adriamycin demonstrates necrosis, with chronic granulation tissue, fibrosis, and epidermal hyperplasia in the surrounding viable tissue; the epidermal atrophy and small vessel occlusion of chronic radiation injury are absent (3,8).

To study this drug-induced injury, we compared intradermal and subpanniculus injections of Adriamycin in rat skin. Injections beneath the panniculus do not cause regular ulceration. In contrast, intradermal injection of Adriamycin produces regular skin necrosis that is dose-related. This ulceration is reliable and reproducible, and can be used as a model for studies of ulcer prevention. Although this ulceration differs from human ulceration in that it is caused by intradermal rather than sc placement, it allows studies of the effect of the drug on living tissue. Probably this same model could be used to study skin effects of other ulcerogenic agents such as the vinca alkaloids and various anthracyclines.

When concentrations of Adriamycin were varied, the most rapid increase in ulcer size occurred when the concentration was increased from 0.010 to 0.020 mg/ml. Even at more dilute concentrations ulceration occurred but to a lesser degree. Increasing dilution of Adriamycin produced less necrosis, suggesting that the more dilute the solution used clinically, the less likely it would be to cause damage. Anecdotal reports conveyed through Adria Laboratories have indicated that in a few instances, infiltration of an extravasated area with saline led to no ulceration of human skin where otherwise ulceration might have occurred. Unfortunately, the dilutions required to reduce drug concentration to a

level where ulceration would be reduced would be enormous; it would take 10 liters of iv solution for a standard clinical dose of approximately 100 mg to produce a concentration of < 0.010 mg/ml.

Ulcers caused by Adriamycin heal at a slower rate in rats than do wounds created by skin excision, even though the surgical wounds are larger. This reduced rate of wound contraction in Adriamycin-induced ulcers is like that found in man (3,4). If the necrotic skin is surgically removed at 2 weeks, ulcers heal faster than if the eschar is left in place. Slower healing with an eschar present is probably due to the splinting effect of the necrotic skin. If a granulating wound is splinted open with a rigid piece of material, the edges will be kept from the usual centripetal movement of wound contraction (9).

The cause of ulceration, and of its slower rate of healing, remains to be determined. Silvestrini et al (10) demonstrated that Adriamycin binds directly to the bases of DNA. Hence, Adriamycin presumably interferes with nuclear function and cell replication necessary for healing. While this theory would explain the death of cells, it does not explain the slower rate of healing of the ulcerations.

A factor in the reduced rate of healing of Adriamycin-induced ulcers may be direct interference with the wound-contraction mechanism. Electron microscopic studies by Jaenke (11) have shown that in the cardiomyopathy of Adriamycin, not only is there direct damage to the nuclei, but also disorganization of the intracellular contractile myofilaments. Recent studies in normal contracting wounds have shown the presence of modified fibroblasts which contain intracellular contractile bundles (12). Since Adriamycin can damage myofilaments in cardiac muscle, possibly contractile fibroblasts in skin ulcers would be similarly damaged. We are planning electron microscopic studies using our rat model to determine if contractile fibroblasts are present in Adriamycin injury and, if so, to evaluate the integrity of the contractile mechanism.

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Hormonal Therapy With Tamoxifen in Male Breast Cancer [1]

Brief Reports and Preliminary Communications

G. N. Hortobagyi,* A. DiStefano, S. S. Legha, A. U. Buzdar, and G. R. Blumenschein [2]

Male breast cancer is responsive to hormonal manipulations. Orchiectomy represents the most effective form of hormonal therapy (1,2). Because of the small number of cases seen by any one individual group, information regarding the treatment of male breast cancer is sporadic and often deficient. This is particularly apparent in the treatment of metastatic disease. We would like to report on two male patients with breast cancer treated with tamoxifen.

Patient 1

Patient 1, a 77-year-old black male with multiple serious medical problems (diabetes, hypertensive cardiovascular disease, and two previous cerebrovascular accidents), was first seen at the Medical Breast Clinic at M. D. Anderson Hospital in September 1977. His primary breast cancer was diagnosed in August 1974, but because of his age, severe intercurrent disease, and reluctance to undergo surgery, no primary treatment was performed. At the time of his first visit to our clinic he was beyond the possibility of surgical or radiation cure. A flat ulcerated tumor plaque replaced the left anterior chest wall extending as far as the axilla, as well as the surrounding abdominal and right anterior chest walls. Two large, mobile, firm lymph nodes were palpated in the left axilla. Multiple satellite lesions were present in the remaining areas of the anterior trunk. Orchiectomy was recommended to the patient but he refused the procedure. Because of reported activity of tamoxifen in female breast cancer, hormonal therapy with tamoxifen (10 mg bid) was started. Treatment with this drug was well-tolerated and was without any side effects or toxicity. Four weeks after starting therapy there was a definite decrease in the number and size of lesions as well as a softening of the leathery anterior chest wall plaque. At this time, axillary lymph nodes were no longer palpable. Three months after starting treatment with tamoxifen, the previously described soft tissue lesions had completely resolved. A full staging workup prior to starting therapy and at the time complete remission was observed showed no other evidence of metastatic disease. In May 1978, the patient had another stroke and he discontinued tamoxifen therapy at that point. Two months later another episode of cerebral ischemia occurred. Since then he has been bedridden and unable to come for followup examination. In August 1978, his disease began to relapse locally. At the present time he is alive with local recurrence and tamoxifen has been re-instituted. Estrogen-receptor assay was not performed.

Patient 2

Patient 2, a 62-year-old white male, was first seen at the Medical Breast Clinic on May 31, 1978. His history dated back to July 1975 when he was first seen with stage IV breast cancer (large right breast tumor, multiple supraclavicular nodes, interstitial nodular metastases on chest roentgenogram, and multiple metastatic lesions on bone scan). Anorexia and a 40-lb weight loss accompanied the presenting symptoms. On January 26, 1976, a wide excision of the right chest wall tumor revealed a primary invasive papillary duct cell carcinoma. In February 1976, a bilateral orchiectomy was performed. This was followed by an excellent response with improvement of performance status to normal, disappearance of soft tissue metastases, and decrease in size of lung metastases. Premorbid weight was regained. The response to orchiectomy continued until July 1977 when pain in the posterior right thigh appeared. No objective changes were found although the symptoms continued. In January 1978, a recurrent right supraclavicular adenopathy became

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apparent and progression of pulmonary metastases was detected. Because of his refusal to receive further ablative therapy, the patient began receiving a standard regimen of cyclophosphamide, methotrexate, and 5-fluorouracil, of which he received two courses without apparent response. In March 1978, weakness in the lower extremities prompted a myelogram which showed extradural effects at the L-2, L-3 level. Radiation therapy and high-dose corticosteroids were started with excellent response. His first evaluation at M. D. Anderson Hospital revealed no evidence of local recurrence. The chest roentgenogram showed diffuse nodular metastases in both lungs and the bone survey revealed disseminated (lytic and blastic) metastases throughout the skeleton. A liver scan was normal. The initial alkaline phosphatase level was 140 units/100 ml and the carcinoembryonic antigen level was 30.6 ng/ml. The rest of the liver function tests and the hematologic survey were found to be within normal limits. On June 2, 1978, tamoxifen (10 mg bid) was started. Successive evaluations in September and December 1978 showed stability of his disease including lung and bone metastases and carcinoembryonic antigen level. His alkaline phosphatase had decreased to 104 units/100 ml and his performance status had improved to almost normal; the patient returned to work. He continued receiving tamoxifen and while no objective regression of tumor has been observed, there has been a definite symptomatic improvement. No estrogen-receptor data were available.

The effectiveness of tamoxifen in metastatic breast cancer of the female breast is well-known (3). The mild side effects and virtual lack of serious toxicity of this drug have been well-documented (4). Information about the effectiveness of different modalities of treatment in male breast cancer is more scanty. It is believed that bilateral orchiectomy is the most effective form of hormonal therapy for male breast cancer (1,5,6). Adrenalectomy, hypophysectomy, and estrogen therapy have also been known to be effective (2,5,6). Selection of patients with hormone-responsive tumors has become more accurate in women with breast cancer with the use of estrogen-receptor assays (3). In at least 24 male patients breast cancer specimens have been assayed for estrogen receptors (7–11) and in ten male patients specimens have been assayed for progesterone receptors (7,8), but correlation of estrogen-receptor status with response to hormonal therapy has not been reported. Since it is reported that > 80% of male breast cancers have a high estrogen-receptor content, a therapeutic trial with antiestrogens appears in order. The total reported experience with tamoxifen in male breast cancer comprises four case reports (seven patients) (12–15). With the patients reported here, a total of nine patients have been treated with tamoxifen and reported in the literature. Of these, six patients have achieved an objective regression and three have not. In addition, another patient was treated with clomiphene, a drug also used as an antiestrogen, and achieved an objective remission (16). None of these patients had estrogen-receptor assays performed. It is of interest that none of the six responders to tamoxifen had prior hormonal manipulation. Although bilateral orchiectomy is a simple surgical procedure virtually devoid of complications, it is often rejected by patients for psychologic or cultural reasons. Secondary ablative procedures and treatment with estrogens, especially in older patients, have a significant incidence of complications. In view of these encouraging results with tamoxifen, more extensive clinical trials with this drug are warranted to assess its place in the treatment of male breast cancer. Correlation of hormonal receptors and response to the different modalities of hormonal manipulation is needed. The excellent tolerance and lack of serious side effects make tamoxifen an attractive alternative to other forms of systemic therapy.

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cis-Dichlorodiammineplatinum(II) in Small Cell Anaplastic Bronchogenic Carcinoma: A Phase II Study [1,2,3]

Brief Reports and Preliminary Communications

Per Dombernowsky,* Sverre Sörenson, Joseph Aisner, and Heine Høi Hansen [4]

cis-Dichlorodiammineplatinum(II) (*cis*-DDP) is one of the first inorganic antineoplastic compounds to be evaluated for activity against human neoplasms (1). *cis*-DDP is a coordination complex which has shown significant activity in experimental tumor models. Phase I studies have been completed suggesting that the dose-limiting toxicity is nephrotoxicity.

In phase II studies *cis*-DDP has been shown to be highly effective against testicular cancers and to have some activity against ovarian, bladder, and head and neck cancers (1–8). Phase II information on the effect of *cis*-DDP in the specific subtypes of bronchogenic carcinoma, especially small cell anaplastic carcinoma, is scarce (9). The present study was therefore undertaken to investigate the activity of *cis*-DDP in small cell anaplastic bronchogenic carcinoma at various dose levels including high dose with forced hydration and diuresis.

MATERIALS AND METHODS

Twenty-seven patients with histologically verified and one patient with cytologically verified small cell anaplastic bronchogenic carcinoma were included in the study. All patients had had progression of disease after conventional therapy.

Eligibility criteria included a measurable or evaluable lesion, an anticipated survival of at least 4 weeks, and complete hematologic recovery from toxicity due to previous chemotherapy or radiotherapy. The wbc count had to be $> 4000/\mu l$ and the platelet count had to be $> 100{,}000/\mu l$ unless bone marrow involvement was documented. Renal function tests had to be normal, defined as a serum creatinine level of < 100 μmols/liter, normal endogenous creatinine clearance or normal EDTA ^{51}Cr clearance, normal BUN level, and normal serum uric acid level. Pretreatment audiograms were obtained in most cases.

The starting dose of *cis*-DDP was 30 mg/m^2 given at 3-week intervals. Doses were subsequently escalated to 45, 60, and 90 or 100 mg/m^2. Patients were treated at only one dose level. For the first three dose levels (30, 45, and 60 mg/m^2) *cis*-DDP was dissolved in sterile water to a concentration of 1 mg/ml and given as a bolus injection without further hydration or diuresis. The higher dose levels of *cis*-DDP (90 or 100 mg/m^2) were given in connection with either furosemide (20–80 mg iv), mannitol (15–37.5 g iv), or both as well as 3–6-liter hydration.

The patients had weekly evaluation of wbc and platelet counts, hemoglobin, serum electrolytes, serum creatinine, BUN, and serum uric acid. Prerequisites for a new course of therapy were normal serum creatinine and BUN levels.

Partial remission was defined as a reduction by 50% of the product of the longest perpendicular diameters of measurable lesions and by 75% of evaluable lesions lasting a minimum of 30 days. Progressive disease was defined as an increase of at least 25% in the size of any measured lesion or the appearance of new lesions.

RESULTS

Twenty-three patients treated with *cis*-DDP were males and five were females, with a median age of 57 years (range, 39–74 years). Minimal prior therapy included combination chemotherapy and/or single-agent treatment with at least four of the following drugs: cyclophosphamide, CCNU, vincristine, vin-

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TABLE 1.—*cis*-DDP treatment results and toxicity in 28 patients with small cell anaplastic carcinoma

Dose level (mg/m^2)	No. of patients	Median No. of courses (range)	No. of partial responses (duration)	No. of patients with toxicity/No. treated *				
				Leukopenia	Thrombocytopenia	Anemia	Gastrointestinal toxicity	Nephrotoxicity
30	7	3 (1–9)	0	2/7	1/7	1/7	7/7	1/7
45	4	4 (3–6)	1 (151 days)	1/4	1/4	2/4	4/4	0/4
60	9	3 (1–6)	2 (24 and 51 days)	4/9	4/9	4/9	8/9	1/9
90†	3	1 (1)	0	1/3	1/3	0/3	3/3	1/3
100†	5	1 (1–2)	0	3/5	2/5	1/5	2/5	1/5
	28	2 (1–9)	3 (12%)	39%	32%	29%	86%	14%

* Leukopenia = wbc count < 4000/μl; thrombocytopenia = platelet count < 100,000/μl; anemia = hemoglobin < 7.0 mmols/liter; gastrointestinal toxicity = nausea and vomiting; nephrotoxicity = serum creatinine level > 120 μmols/liter.
† With forced diuresis.

blastine, methotrexate, adriamycin, VP-16-213, procarbazine, streptozotocin, or prednimustine. Ten patients also had received irradiation.

Measurable parameters consisted of a chest lesion in 25 patients, enlarged peripheral lymph nodes in eight, and liver metastases in four. Furthermore, 13 patients had a positive bone marrow examination.

The number of patients treated at the different dose levels, the number of courses of *cis*-DDP, the treatment results, and the toxicity are summarized in table 1. The median number of treatment courses was two with a range of one to nine and the duration of treatment was 16–183 days.

Of the eight patients treated with high-dose *cis*-DDP, six received only one course of therapy. In three of these patients this was due to progression of the disease. In two patients additional *cis*-DDP was not given due to severe thrombocytopenia (21,000 and 24,000 cells/μl), while the last patient received only one course due to severe nephrotoxicity.

Partial responses were observed in two patients with measurable disease treated with 45 and 60 mg/m^2 of *cis*-DDP respectively. One patient, a 65-year-old female treated with 45 mg/m^2, had a partial response of a chest lesion continuing for 151 days. One short-lived partial remission (51 days) was observed in a 47-year-old male. In addition, one patient had > 50% tumor shrinkage but the duration of response was only 24 days. These three responding patients had previously received chemotherapy with combinations of cyclophosphamide, CCNU, vincristine, and methotrexate as well as VP-16-213 and adriamycin. It should be noted that none of the patients treated at the higher dose levels with hydration and forced diuresis showed any response.

Toxicity

The hematologic toxicity was generally modest and was not correlated to bone marrow involvement. A decrease in the leukocyte counts to < 4000/μl was observed in nine patients (32%) and in one patient a value of 1200/μl was found. Platelet counts < 100,000/μl were observed in eight patients (28%); in three of these, values < 50,000/μl were found, with the lowest value being 21,000/μl without apparent bleeding. Moderate anemia (hemoglobin < 7.0 mmols/liter) was seen in eight (29%) of the patients.

Instant and severe nausea and vomiting, continuing up to 24 hours, was present in 24 (86%) of the patients. The gastrointestinal symptoms were usually refractory to conventional antiemetics.

The most important dose-limiting toxicity consisted of nephrotoxicity with a pronounced but transient elevation of serum creatinine and BUN levels in four (14%) of the patients. One patient treated at the 30-mg/m^2 level developed a progressive decrease in kidney function after the second *cis*-DDP dose and died with uremia 3 weeks after the last dose. Another patient treated at the 90-mg/m^2 level developed an increase in the serum creatinine level from 106 μmols/liter (normal = < 120 μmols/liter) to 580 μmols/liter in 8 days, and his potassium increased to 7.3 μmols/liter (normal = 3.5–5.0 μmols/liter). Kidney function slowly improved in 1 week, while endogenous creatinine clearance remained at 23% of the starting value.

DISCUSSION

Phase I clinical trials with *cis*-DDP have been performed mainly with a 5-day fractionated or a

single-dose schedule every 3 weeks and no definite difference in toxicity or response has been observed (1,2,4,10–13). This is in agreement with investigations carried out in the murine L1210 leukemia system where no schedule-dependency was observed (1).

In bronchogenic carcinoma, data from 50 patients treated with *cis*-DDP have been collected (2–4,9–13). Histologic cell types, however, were not always stated, and responses were described in only two patients, one with squamous cell carcinoma (4) and one with adenocarcinoma (2). Among four patients with small cell anaplastic carcinoma no responses were observed at a dose level of 75 mg/m^2 given every 3 weeks (9).

In the present study, one short-lived partial response (54 days) and one very short-lived response (24 days) were seen at 60 mg/m^2 and one partial response of 151 days' duration was seen at the 45-mg/m^2 dose level. The hematologic toxicity was modest and acceptable, but we observed pronounced nephrotoxicity. Neither the hematologic toxicity nor the nephrotoxicity was dose-dependent.

Considering the severe refractory nausea and vomiting and the minimal response rate with this agent, we feel that *cis*-DDP has no major role as a single agent in the treatment of patients with small cell anaplastic bronchogenic carcinoma. Further studies with this drug as a single agent in this disease do not seem warranted at this time. Should it become feasible to control both the nausea and vomiting and the nephrotoxicity, the role of *cis*-DDP in combination with other agents may need to be re-evaluated since synergism has been observed in the L1210 system (1).

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Tetany: A Complication of *cis*-Dichlorodiammineplatinum(II) Therapy [1,2]

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cis-Dichlorodiammineplatinum(II) (CDDP) is an antitumor agent that has been evaluated in clinical trials since 1972. The renal toxicity of this drug, as reflected by increases of serum creatinine and BUN, and the pathologic changes in renal tubules are well-documented (1). Hydration with or without mannitol and diuretics has decreased the severity of renal toxicity induced by CDDP (1,2).

Hypomagnesemia and hypocalcemia with tetany have not previously been reported with this compound. We have observed hypomagnesemia in 15 of 16 evaluable patients receiving CDDP therapy for solid tumors, and in four of eight children with neuroblastoma, associated hypocalcemia and tetany occurred.

METHODS AND MATERIALS

Twenty-two children with solid tumors resistant to conventional chemotherapy were treated with CDDP at doses of 90 mg/m^2 every 3 weeks or 30 mg/m^2/week. The eight children with neuroblastoma ranged in age from 2 years and 8 months to 9 years and 11 months (median, 3 years and 7 months), with only one child $>$ 6 years old. The 14 children with other solid tumors ranged in age from 1 year and 8 months to 20 years and 7 months (median, 13 years), with only one child $<$ 6 years old.

CDDP was infused over 6 hours with iv fluids and mannitol being given for 2 hours before and during the 6-hour infusion. Lasix was given after the first 2 hours of hydration. All patients had blood drawn before each infusion for serum creatinine, BUN, electrolytes, and calcium. Before the first case of tetany occurred, the importance of measuring serum magnesium levels was not appreciated. Subsequently, these levels were determined in the eight children with neuroblastoma and in eight of the 14 children with other tumors.

RENAL TOXICITY RESULTS

Neuroblastoma

All eight children had normal serum creatinine, BUN, calcium, and electrolyte values upon entering the study. In five patients the pre-CDDP serum magnesium was measured and was normal (1.4–1.9 mEq/liter).

Transient increases of BUN of $>$ 20 mg/100 ml occurred in seven of eight children but serum creatinine, uric acid, and bicarbonate remained normal. Although the urine output was not measured with each infusion, all children excreted large volumes of urine in response to the mannitol and lasix.

Four of the five children who had normal pretreatment serum magnesium levels had decreases with the first dose of CDDP (two children had received 90 mg/m^2 and two children had received 30 mg/m^2), while the fifth child developed hypomagnesemia after the third infusion of CDDP at 30 mg/m^2. Three children had serum magnesium levels obtained for the first time 6 weeks after receiving the first dose of CDDP at 90 mg/m^2. All three had abnormally low serum levels. Serum magnesium levels of $\leq$ 1 mEq/liter occurred in six of eight children. In four children, serum calcium levels remained normal and no clinical tetany was observed. However, in four other children, serum calcium levels of $<$ 8.5 mg/100 ml were observed and clinical signs and symptoms of tetany, with severe carpopedal spasm, developed. Tetany occurred with the second dose of CDDP at 30 mg/m^2 in a child who received two phosphate-containing enemas the day tetany developed. The other three episodes of tetany occurred 6, 7, and 10 weeks after CDDP therapy was started. No precipitating factors could be found; however, all three children had very poor nutritional intake in the week prior to the onset of tetany. The tetany resolved with parenteral administration of magnesium and calcium. In three children symptoms did not recur once magnesium sup-

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plements were instituted, even though normal serum values for magnesium were not maintained. A fourth child had severe electrolyte problems and required 1 month of nasogastric and parenteral supplementation of magnesium before oral supplements controlled the symptoms of tetany.

One of the four children with asymptomatic hypomagnesemia was given supplemental oral magnesium after four doses of CDDP at 90 mg/m^2. The magnesium level returned to normal and remained there during continued CDDP infusion. In two of the three children without supplementation the serum magnesium levels returned to normal 7 weeks after CDDP was discontinued, while one child had a persistently decreased serum magnesium level at last followup 4 weeks after discontinuation of CDDP.

Other Solid Tumors

Transient increases of BUN of $>$ 20 mg/100 ml occurred in four of eight patients receiving CDDP at 90 mg/m^2 and in none of six receiving CDDP at 30 mg/m^2. Serum creatinine levels remained normal.

Seven of the eight patients (three who received 30 mg/m^2 and five who received 90 mg/m^2) evaluated for hypomagnesemia had values of $<$ 1.4 mEq/liter. Only one child developed transient paresthesias of her hands and lips after administration of a phosphate-containing enema. This child plus one other asymptomatic child were the only patients in this group of 14 children who had serum calcium values of $<$ 8.5 mg/100 ml. Both patients had received CDDP at 30 mg/m^2.

DISCUSSION

Hypomagnesemic-hypocalcemic tetany has not previously been reported in association with CDDP therapy. Renal tubular re-absorption of magnesium is efficient and it is difficult to produce symptomatic hypomagnesemia in adults with normal renal function (3). However, if renal tubular damage prevents normal re-absorption of this cation, magnesium will be lost in the urine. Tubular damage by CDDP is the most likely primary cause for the hypomagnesemia observed in our patients.

Although tetany may occur with hypomagnesemia alone, it was observed in our patients only if hypocalcemia was also present. The hypocalcemia could also have resulted from excessive urinary loss of the cation; however, another possible mechanism is the decreased synthesis and/or release of parathyroid hormone which is known to occur if serum magnesium levels are low (4,5).

Although hypomagnesemia was documented in eight of eight patients with neuroblastoma and in seven of eight evaluable patients with other tumors, severe carpopedal spasm was observed only in the younger children with neuroblastoma. Renal toxicity based on serum creatinine was not observed in either group of patients, nor was nausea and vomiting any greater in one group compared to the other. Except for the child who received phosphate-containing enemas, no exogenous factors known to interfere with calcium homeostasis were present in the symptomatic patients. No tumor response was observed in three symptomatic patients, making endogenous release of phosphate an unlikely cause for the hypocalcemia.

One obvious difference between the children with neuroblastoma, who had a 50% incidence of tetany, and the children with other tumors is their age, and therefore their total body stores of cations. In the face of excessive loss, any minor decrease in the oral intake may upset normal cation balance much more easily in the smaller child whose body stores are limited. All children, especially the very young, receiving CDDP therapy should be closely monitored for hypomagnesemia. Parents and physicians should be aware that tetany may occur and that parenteral administration of magnesium rather than calcium is needed to reverse the symptoms.

We are currently evaluating urinary loss of cations, intracellular magnesium levels, and parathyroid hormone levels serially in children with neuroblastoma receiving CDDP to determine the mechanism by which this electrolyte imbalance occurs and also to see if oral magnesium supplementation can prevent this complication of CDDP therapy.

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Phase II Evaluation of Chlorozotocin in Patients With Non-Small Cell Carcinoma of the Lung [1,2,3]

Brief Reports and Preliminary Communications

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Chlorozotocin is a water-soluble chloroethyl nitrosourea with demonstrated activity in several animal tumor systems including L1210 and P388 leukemias and B16 melanoma.[6] Phase I studies indicated that a single dose of 120 mg/m^2 or divided doses of 150–200 mg/m^2 given over 5 days produced acceptable myelosuppression, primarily manifested as thrombocytopenia (1–3), with less nausea and vomiting on the 5-day schedule (4). Pharmacokinetic studies have shown that the drug is rapidly cleared from the plasma with a terminal half-life of approximately 30 minutes and that about 50% of the dose is excreted by the kidneys (1). Occasional objective responses have been reported in Hodgkin's disease (3), nodular lymphoma (1), chronic lymphocytic leukemia (5), melanoma (1,2,5), and carcinomas of the colon (5), breast (5), kidney (2,3), ovary (3), and lung (1,3,5). Because of the reported activity of the lipid-soluble nitrosoureas in non-small cell carcinoma of the lung (6–8), a phase II trial of chlorozotocin in this disease was undertaken.

MATERIALS AND METHODS

Thirty-five patients were enlisted in the study between March 1977 and March 1978. All patients had objectively measurable disease and histologic confirmation of the diagnosis of non-small cell carcinoma of the lung. A performance status (PS) (Karnofsky scale) of ≥ 50%, a platelet count of ≥ 100,000/mm^3, a wbc count of ≥ 4000/mm^3, and normal hepatic and renal function were required for entry in this study. Thirty patients were evaluable for therapeutic response. The median age of the patients was 61 years (range, 34–77 years) and the median PS was 60% (range, 50%–90%). Seventeen patients had received prior chemotherapy (none had received other nitrosoureas), including four who had been treated with radiation as well, two patients had received prior radiotherapy alone, and 11 patients had not had previous treatment. The evaluable patients included 18 with adenocarcinoma, 11 with epidermoid carcinoma, and one with large cell anaplastic carcinoma.

Patients were considered evaluable 6 weeks after the initiation of chlorozotocin therapy. Therapeutic responses were defined as: *complete remission*—a disappearance of all measurable lesions for at least 1 month; *partial remission (PR)*—a ≥ 50% reduction of all measurable lesions for at least 1 month; and *minor response*—a > 20% reduction of all measurable lesions, but less than that required for a PR.

Chlorozotocin was administered as a rapid iv injection through a running iv line in equally divided doses for 5 consecutive days. Initial total doses were 200 mg/m^2 for previously untreated patients with a PS of ≥ 70%, 175 mg/m^2 for patients with a PS of ≥ 70% who had received prior chemotherapy, and 150 mg/m^2 for patients with a PS of ≤ 60%. Courses were repeated every 6 weeks. If the platelet count fell to < 50,000/mm^3 or if the wbc count nadir was < 2000/mm^3, the next course of chlorozotocin was given at a total dose which was 25 mg/m^2 lower than that of the previous course. If no myelosuppression occurred, the subsequent course was given at a total dose which was 25 mg/m^2 higher than that of the previous course, but not > 200 mg/m^2. Recycling of therapy was delayed in all patients until the platelet count returned to ≥ 100,000/mm^3 and the wbc count rose to ≥ 3500/mm^3.

RESULTS

Therapeutic responses.—Two PRs were noted in the 30 (7%) evaluable patients. One occurred in a

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[3]Chlorozotocin was supplied by the Division of Cancer Treatment, National Cancer Institute, Bethesda, Md.

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[5]We wish to thank Kathleen Trainor for preparation of the manuscript and Orlando Hernandez for assistance with analysis of the data.

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TABLE 1.—Hematologic toxicity in 30 patients with non-small cell lung cancer treated with chlorozotocin

Total 5-day dose (mg/m^2)*	No. of courses	Wbc count nadir (cells × $10^3/mm^3$)			Platelet count nadir (cells × $10^3/mm^3$)		
		Median	Range	Median Day	Median	Range	Median Day
150	18	5.2	2.4–11.0	28	143	93–209	28
175	24	4.9	3.3–7.5	42	83	16–226	28
200	12	3.7	2.6–5.0	34	44	17–190	29

* Drug administered as 5 equal daily doses.

patient with epidermoid carcinoma who had failed to respond to previous chemotherapy and had a PS of 90%. This patient experienced a > 90% reduction in his pulmonary lesions which continues at 12 months. The other PR occurred in nodal and subcutaneous metastases of a previously untreated patient who had adenocarcinoma and a PS of 70%. The duration of this response was 2½ months. Both patients experienced only mild toxic reactions consisting of thrombocytopenia (platelet count nadirs of 55,000 and 80,000/mm^3, respectively). There was one minor response in a previously untreated patient with epidermoid carcinoma and three minor responses in patients with adenocarcinoma (one was previously untreated, one had had previous radiotherapy, and one had had prior chemotherapy and radiotherapy). No complete remissions occurred.

Toxicity.—A median of two courses was given to each patient (range, one to six courses). The major toxic effect was myelosuppression as outlined in table 1. Thrombocytopenia was the dose-limiting hematologic abnormality. No cumulative hematologic toxicity was observed. No hospitalizations were required as a result of myelosuppression although three outpatients received platelet transfusions. There was no drug-related sepsis or death. Mild nausea and vomiting occurred in < 10% of patients. There were no occurrences of hyperglycemia or hepatic or renal dysfunction noted in association with chlorozotocin therapy in this study.

DISCUSSION

Clinical evaluations of BCNU, CCNU, and methyl-CCNU in non-small cell lung cancer have shown response rates in the range of 3%–25% (6–8). Chlorozotocin, a new water-soluble chloroethyl nitrosourea with high alkylating and low carbamoylating activities (9), was introduced into clinical trials to evaluate its efficacy in a variety of human malignancies.

This phase II trial included patients with good PSs. Thirteen of 30 (43%) patients had not received prior chemotherapy, and all were outpatients. Although myelosuppression occurred, only two of 30 (7%) adequately treated patients had major objective responses. At 95% confidence limits, the predicted true response rate is 2%–18%. We conclude that chlorozotocin, when given in the present dose and schedule, is only a marginally effective agent in the treatment of non-small cell carcinoma of the lung, and that it offers no therapeutic advantage over the nitrosoureas currently used in the treatment of this disease.

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LETTERS

Long-Term Treatment With *cis*-Dichlorodiammineplatinum(II)-Vinblastine-Bleomycin: Possible Association With Severe Coronary Artery Disease

We have recently seen two young males with no evident risk factors for the development of atherosclerosis who had histologic evidence of severe coronary artery disease (CAD) at autopsy following the long-term administration of *cis*-dichlorodiammineplatinum(II) (CDDP), vinblastine (VBL), and bleomycin (BLEO) for the treatment of metastatic testicular carcinoma.

CASE REPORTS

Patient 1

A 20-year-old white male underwent inguinal orchiectomy for embryonal carcinoma of the testis. Physical examination, routine laboratory studies, and electrocardiogram (ECG) were normal. He received adjuvant actinomycin D for 4 months and was then found to have an excisional biopsy-proven pulmonary metastasis. Actinomycin D, methotrexate, and chlorambucil (Leukeran) were administered for 8 months, but because of the appearance of new pulmonary metastases, the patient was referred to Baylor College of Medicine (Houston, Tex). Physical examination, an ECG, and laboratory studies were normal with the exception of three nodules in the right lung seen on the chest roentgenogram. CDDP at a dose of 15 mg/m²/day iv on Days 1–5, VBL at a dose of 12 mg/m² iv on Day 1, and BLEO at a dose of 15 units iv biweekly every 28 days was begun. Following the first course of chemotherapy, the pulmonary nodules regressed completely. The patient was in complete remission for 9 months when he developed a metastatic lesion in the cerebellum and recurrence of the pulmonary nodules. Chemotherapy was interrupted (total dose, 600 mg/m² of CDDP, 96 mg/m² of VBL, and 200 units/m² of BLEO) and he received 4000 rads of whole-brain irradiation, during which he developed progressive ascending extradural thoracic spinal cord compression unresponsive to 4000 rads of irradiation and died. At autopsy, there was severe atherosclerosis of the coronary arteries: 40% proximal right, 75% posterior descending, 75% first diagonal, and 60% left anterior descending coronary artery occlusion. There was no evidence of atherosclerosis of the other major vessels.

Patient 2

A 25-year-old white male underwent inguinal orchiectomy for mixed embryonal and teratocarcinoma of the testis which was also found in one lymph node removed at the time of retroperitoneal lymphadenectomy 1 week later. He received adjuvant actinomycin D for 8 months and was lost to followup. Thirteen months later he developed a metastatic left pelvic mass, bilateral supraclavicular lymphadenopathy, and subcutaneous nodules. His cardiovascular examination and ECG were normal. He began to receive 15 mg/m²/day of CDDP iv on Days 1–5, 12 mg/m² of VBL iv on Day 1, and 15 units of BLEO biweekly every 28 days. After 1 year of asymptomatic partial remission the patient developed bilateral ureteral obstruction and hepatic failure due to extensive metastases and died. The total drug doses administered were: 600 mg/m² of CDDP, 84 mg/m² of VBL, and 200 units/m² of BLEO. A postmortem examination demonstrated triple-vessel atheromatous stenosis: 80% proximal left circumflex, 50% proximal left anterior descending, and 30% right coronary artery. There was no evidence of atherosclerosis of other major vessels or of pericardial or myocardial metastases.

Neither of these two patients was obese, diabetic, hyperlipidemic, or hypertensive, and neither had a family history of early CAD. The first patient received a maximum total dose of 1600 rads (calculated from isodose curves) of ionizing radiation to the posterior aspect of the heart during the 4 weeks immediately prior to death. The second patient was a 15 packs/year cigarette smoker. We do not consider either of these to be significant risk factors for the development of coronary atherosclerosis (1,2).

COMMENT

To date, no cancer chemotherapeutic agents have been shown to accelerate the development of atheromatous lesions or place the patient at increased risk for the development of CAD. Although there have been several reports of angina or myocardial infarction within hours after the iv infusion of both 5-fluorouracil (3,4) and vincristine (5–7), no similar effects of VBL administration have been observed.

Coronary insufficiency from vincristine is presumably due to either a coronary arterial spasm or an acute decrease in ventricular contractility, since postmortem examination in those patients dying of their infarction or coronary cineangiography in those surviving has shown no evidence of CAD.

Extensive clinical experience with the long-term use of actinomycin D, VBL, and BLEO, both alone and in combination, has been accrued; no association with CAD has been reported. However, experience with CDDP, particularly in long-term administration, is limited. No studies in either animals or man implicate CDDP as a potentiating agent in the development of accelerated atherosclerosis.

Since CDDP in combination with VBL and BLEO is proving to be useful in the adjuvant therapy for testicular malignancies, confirmation of accelerated atherosclerosis as a possible dose-related effect of long-term administration should be sought. The purpose of this letter is to alert clinical investigators to this possible relationship.

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Contracture Formation Secondary to Bleomycin[1]

The pulmonary and epidermal side effects of bleomycin are well-established. Heretofore, there have been no reported cases of contracture formation secondary to bleomycin therapy. We wish to report the first such occurrence in a child with xeroderma pigmentosum (XP).

CASE REPORT

A white male (13 years and 11 months old) was referred to the M. D. Anderson Hospital and Tumor Institute in September 1975 with a diagnosis of XP. He had received prior treatment for multiple epidermoid carcinomas that had consisted of surgical removal of a total of 18 lesions followed by either surface radium (10-mg) needle treatments or irradiation (3000–6800 rads) on each occasion. From September 1975 to January 1976, he had a right shoulder-to-chin flap constructed. During each stage of the reconstructive surgery, numerous skin biopsies were performed which revealed nine squamous cell carcinomas and one basal cell carcinoma.

Due to the continual recurrence of squamous cell carcinomas, a trial of bleomycin was undertaken. Fifteen units were given sc semiweekly for 6 weeks (0.4 mg/kg). After a 6-week rest period, additional courses were administered. A total cumulative dose of 300 mg/m^2 was administered from April to October 1976. During the last 6 weeks of bleomycin administration, the parents noted the progressive development of contractures of the child's fingers. Our examination revealed a full range of motion of the elbows and wrists. There were moderate flexion contractures of the metacarpophalangeal and interphalangeal joints of the fingers, which were worse on the right hand than on the left. The thumbs were not involved. No muscular, neurologic, or neuromuscular impairment of the hands or forearms was present. Vigorous physical therapy was undertaken and further doses of bleomycin were discontinued. Prior to the development of the contractures, no treatment to the arms (ie, surgical excisions, irradiation, or skin grafting) was administered, apart from the construction of the aforementioned right shoulder-to-chin flap. To date, although the flexion contractures persist, no new contractures have been noted.

Since the termination of bleomycin, our patient has undergone seven subsequent surgical proce-

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dures for plastic surgical revisions and/or the removal of newly formed skin lesions. Nine squamous cell carcinomas and three basal cell carcinomas have been removed. There was, however, evidence of arrest of progression of his lesions during bleomycin therapy.

DISCUSSION

XP is an autosomal recessive disease characterized by photosensitivity, a defect of DNA repair, and a high incidence of skin malignancies (1). Of the latter, junctional nevi, basal cell or squamous cell carcinomas, and melanomas predominate (2). Some patients have been shown to have neurologic abnormalities but the development of primary contractures is not a reported sequela of this disease entity. Our decision to use bleomycin was based upon a report of response in a patient with XP and several reports in the literature indicating responses of squamous cell carcinomas to this agent (3–11). The documented side effects from bleomycin therapy are many, the most prominent of which include pulmonary fibrosis, skin and mucous membrane reactions, and idiosyncratic reactions.[2] The skin reactions include erythema, rash, striae, vesiculation, hyperpigmentation, tenderness, hyperkeratosis, nail changes, alopecia, pruritis, and stomatitis. No previous reports of contracture formation following therapy with bleomycin exist. There was a 5-month lapse from the initial use of bleomycin to the formation of our patient's flexion contractures. The lack of subsequent contracture formation after termination of bleomycin therapy in this child and the absence of reported cases of contracture formation in patients with XP strongly suggest that contracture formation was related to the effects of bleomycin in connective tissues. Our patient did not have signs of pulmonary fibrosis (either radiographic or pulmonary function). Since contracture formation has not been reported with bleomycin before, this effect might be peculiar to XP.

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[2]Package insert for Blenoxane (sterile bleomycin sulfate). Syracuse, NY, Bristol Laboratories.

Phase II Trial of Dianhydrogalactitol in Advanced Soft Tissue and Bony Sarcomas: A Southwest Oncology Group Study[1]

Dibromodulcitol and dibromomannitol, dibromohexitols which have known cytostatic effects on tumor cells, are converted in vivo to the corresponding diepoxy derivative which is thought to be responsible for the observed cytostatic effects (1). The corresponding diepoxy form of dibromodulcitol, 1,2:5,6-dianhydrogalactitol (DAG), has recently been synthesized and was shown to act as an alkylating agent in a fashion similar to that of its parent compound (2). DAG was tested in animal tumor systems where it showed significant inhibition of tumor growth and prolongation of survival in five mouse and five rat tumors (3). Phase I trials were carried out using four dose schedules (4,5) and revealed dose-limiting toxicity in the form of myelosuppression, more often affecting platelets than

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leukocytes and more common and severe in patients who had received prior nitrosoureas. Responses were seen in two patients with renal cell carcinoma and in one each with lung adenocarcinoma and laryngeal carcinoma. Phase II trials were undertaken by the Southwest Oncology Group using a schedule of 5 consecutive days every 4 weeks.

MATERIALS AND METHODS

At 12 member institutions of the Southwest Oncology Group, 29 adult patients with biopsy-proven advanced or metastatic soft tissue or bony sarcomas were evaluated. The median age of the patients was 54 years (range, 17–78 years). Sex was evenly distributed, with 15 females and 14 males. The study population consisted of 23 whites, five blacks, and one Indian. At the time of study entry all patients were required to have a leukocyte count of ≥ 4000/μl and a platelet count of ≥ 100,000/μl. No patient was entered until recovery from the effects of prior treatment had occurred. Other patient characteristics are summarized in table 1.

All 29 patients were considered to be evaluable for toxicity. Sixteen of the 29 demonstrated evidence of toxicity, while 13 experienced no toxicity. Myelosuppression occurred in all 16 patients with toxicity.

TABLE 1.—Characteristics of the study patients

Patient characteristic	No. of patients
Histologic type	
Leiomyosarcoma	11
Liposarcoma	4
Fibrosarcoma	2
Rhabdomyosarcoma	2
Osteosarcoma	2
Other	8
Primary site	
Abdomen	11
Lower extremity	8
Other	10
Metastatic site	
Lung	17
Abdomen	8
Skin	7
Liver	6
Nodes	6
Bone	6
Multiple sites	15
Prior treatment	
Surgery	29
Radiotherapy	14
Chemotherapy	28
Immunotherapy	3
Performance status	
80%–100%	11
50%–70%	15
< 50%	3

Fourteen of the 16 experienced leukopenia, with the median lowest recorded leukocyte count of 2400/μl (range, 1500–3900/μl) occurring at a median time of Day 14 (range, Days 6–35) after initiation of drug therapy. The lowest leukocyte count occurred after the first drug course in eight of the 14 patients and after the second course in the other six. Nine of the 16 patients experienced thrombocytopenia, with the median lowest recorded platelet count of 65,000/μl (range, 9000–88,000/μl) occurring at a median time of Day 25 (range, Days 12–35) after initiation of drug therapy. The lowest platelet count developed after the first drug course in seven of the nine patients and after the second course in the other two.

Other adverse effects observed in the study population included nausea and vomiting in three patients (mild in two and moderate in one), mild alopecia in one patient, and confusion in one patient.

In the 29 sarcoma patients in this study, DAG demonstrated no significant efficacy. Although five of the 28 patients evaluable for response did experience stabilization of their disease process, no objective regressions were observed. As in most studies of this nature, the patients had received extensive prior therapy, their diseases were generally far-advanced, and 62% were at least partially bedridden. These factors lessen the chance of patient response to therapy, but some evidence of objective regression should have been seen if this drug has any efficacy in the treatment of sarcomas. That the dose and schedule tested represent an adequate drug trial is evidenced by the fact that myelosuppression of a significant degree was observed in 16 of 29 patients (55%).

As in other reported trials of DAG, adverse effects were manifested mostly as myelosuppression. Since 75% of the patients received two or fewer drug courses, a definite conclusion as to any cumulative effect DAG might exert on bone marrow cannot be reached. Overall toxicity was acceptable.

In conclusion, DAG at the dose and schedule tested is inactive in the second-line treatment of advanced sarcomas.

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Cardiotoxicity of Mitomycin C in Man and Animals

Buzdar et al (1) recently reported the possible synergistic cardiotoxicity of adriamycin (ADR) and mitomycin C (MMC). The authors suggest that enhancement by MMC of the subclinical cardiac damage induced by prior ADR therapy is the probable explanation for the higher incidence of congestive heart failure in MMC-treated patients. They mention that there are no previous reports of MMC as a potential cardiotoxic agent. Yet, in 1975 Suzuki and Niibe (2) reported the occurrence of histologic myocardial changes similar to radiation-induced heart injury in five of 15 patients treated with MMC alone. They suggested that the radiomimetic property of MMC is the probable reason for the observed histologic abnormalities. These investigators did not report, however, whether any of these patients had evidence of congestive heart failure.

Although there is rapid inactivation of iv administered MMC by human heart tissue, high concentrations of MMC are found in the guinea pig heart following iv administration (3). Hemorrhages have been described in the endocardium and pericardium of dogs receiving MMC (4), and a mixed myocarditis with lysis of cardiac muscle fibers leading to sclerosis and mutilation has been demonstrated in Wistar rats (5).

MMC alone may, therefore, be a potentially cardiotoxic agent. Careful observation should be made for instances of potential cardiotoxic synergism between MMC and radiation or ADR.

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Regression of Regionally Confined Melanoma With Intra-Arterial *cis*-Dichlorodiammineplatinum(II) [1,2]

cis-Dichlorodiammineplatinum(II) (*cis*-platinum) is a coordination complex of platinum which was shown by Rosenberg et al (1) to inhibit bacterial growth. Its early use in human testicular neoplasms showed antitumor effectiveness both as a single agent (2) and in combination with other drugs (3). Subsequent trials in other human malignancies also showed encouraging results (4,5).

Melanoma is often refractory to most therapeutic agents (6), but several recent reports documented clinical tumor responses to *cis*-platinum in phase I trials (7–10). Furthermore, *cis*-platinum has a short initial half-life and may bind to tissues on one pass through the capillary bed. We therefore tried to improve its therapeutic index by increasing its local concentration and its gradient across the tumor cell membrane by intra-arterial infusion in patients with regionally confined melanoma. The effectiveness of this technique was initially observed in a melanoma patient who had a partial remission induced by a combination of *cis*-platinum and acti-

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[2]We acknowledge the excellent technical help and utmost devotion of Susan Johnston and Joan Covell in the care of the infusion pumps.

nomycin D administered intra-arterially (11). Since actinomycin D contributed significantly to immediate toxicity and to later myelosuppression, subsequent patients were treated with *cis*-platinum alone.

This paper presents the encouraging results of the first four patients treated with intra-arterial *cis*-platinum.

MATERIALS AND METHODS

Patient characteristics are shown in table 1. Catheters were placed via the Seldinger technique in the femoral artery, with their position being determined fluoroscopically. Patients were hydrated iv 2 hours prior to the arterial infusion, with 300 ml of dextrose-saline supplemented with 20 mEq of KCl, followed by 50 ml of 20% mannitol infused over 15 minutes. The *cis*-platinum was infused by a volumetric infusion pump (Sigma Motor). The pump was initiated and maintained with 500 ml of normal saline mixed with 2000 units of Na heparin at 20 ml/hour.

cis-Platinum was infused at a rate of 150 ml/hour. The drug was mixed with aqueous Na heparin (3000 units) and diluted with saline to 300 ml for doses of < 300 mg or to 450 ml for doses of > 300 mg. During the *cis*-platinum arterial infusion, patients also received 800 ml of dextrose-saline iv supplemented with 20 mEq of KCl iv, along with 200 ml of 20% mannitol over 3–4 hours. Thereafter, they received 2000–3000 ml of dextrose-saline solutions at an approximate rate of 150 ml/hour for 24 hours with careful monitoring of fluid and electrolyte balance. The catheter was pulled out after 4 hours. BUN level, creatinine level, and blood counts were obtained prior to therapy and weekly thereafter in most patients. Courses of therapy were usually repeated at 35-day intervals, and tumor responses were determined prior to each course.

RESULTS

Patient 1 entered complete remission after Day 7 of her second course with 2-cm nodules becoming nonpalpable on the stump of her previously amputated leg. She had previously received adjuvant treatment with continuous arterial infusion of methotrexate (10 years previously) and bacillus Calmette-Guérin (BCG), intralesional methanol-extracted residue of BCG, intralesional *Corynebacterium parvum*, actinomycin D plus DTIC, and maytansine given sequentially.

Patient 3 entered partial remission ($> 50\%$ improvement in the size of all measurable disease), with marked regression of hepatic lesions treated by infusion into the hepatic artery after one course. After the second course a partial response was achieved in both the hepatic lesions and the retroperitoneal lesions (which were not infused) as documented by computerized axial tomographic scan. He had received prior adjuvant treatment with BCG, *C. parvum*, and actinomycin D plus DTIC.

Patient 4 had previously received only BCG and had slight improvement during each of her two courses but has not achieved partial remission of her multiple subcutaneous metastases. Patient 2, who was previously treated with adjuvant intra-arterial perfusion with melphalan, actinomycin D, and mechlorethamine, was stable during her three courses, but her subcutaneous metastases began to increase while she awaited recovery from renal toxicity of the third course.

TABLE 1.—Patient characteristics, treatment dose, and response

Patient No.	Age/ sex	Extent of disease	Response to previous therapy	*cis*-Platinum course No.	Dose (mg/m^2)	Artery	Response
1	80/F	Recurrent melanoma, left leg (2 nodules)	DTIC + actinomycin D + *C. parvum*: no response	1 2	75 120	External iliac	Complete remission by Day 7 of course 2
2	61/F	Multiple cutaneous melanoma, right leg	Perfusion with melphalan, actinomycin D, and mechlorethamine: no response	1 2 3	100 150 150	External iliac	Progression after 3 courses
3	54/M	Liver metastases and retroperitoneal nodes	DTIC + actinomycin D + *C. parvum:* no response	1 2	120 150	Hepatic	Partial remission after 1 course
4	68/F	Multiple lesions, right leg	Intralesional BCG: new lesions appearing	1 2	120 150	External iliac	Improvement with each course

Nephrotoxicity and myelosuppression are recorded in table 2. Fever to 102° F occurred within 24 hours after several courses and resolved spontaneously. No stomatitis or alopecia was observed. Nausea was moderately severe and lasted 12–24 hours. Although ototoxicity has been reported with *cis*-platinum, no changes were observed on audiograms in two patients.

DISCUSSION

Intra-arterial *cis*-platinum is relatively well-tolerated with little mobidity attributable to the arterial technique. Systemic toxicity is qualitatively similar to that seen after iv administration of the drug. Maximum values for BUN and creatinine appear in the first week, with the lowest blood counts appearing in the third week. The average time for recovery is 35 days; courses are therefore recommended at 4–5-week intervals. A dose of 150 mg/m^2 produces acceptable toxicity suggesting that higher doses may be used. At these doses there is an appreciable systemic antitumor effect as was evidenced in patient 3 by the response of retroperitoneal nodes which were not infused directly. The intra-arterial route may therefore be used for regional control of tumor even if disease is suspected outside the infused area.

The response to intra-arterial *cis*-platinum is encouraging. The speed and degree of responses in both subcutaneous and visceral metastases noted in these patients are unusual in our experience. Although we cannot rule out the possibility that similar responses would have occurred with systemic administration of *cis*-platinum, the fact that systemic regression of nodal metastases took longer than regression of infused liver metastases in patient 3 suggests a differential effect on the site infused. On the other hand, arterial infusion (as opposed to isolation perfusion) does allow full systemic therapy, as evidenced by the nodal response in patient 3 and by the systemic toxicity in all patients, while increasing the quality of local response. The latter phenomenon could be accounted for by the increase in the drug concentration gradient across the tumor cell membrane which even if transient may augment antitumor effect. The gratifying results reported here suggest that this approach should be pursued. Further trials of intra-arterial *cis*-platinum in patients with other regionally confined platinum-sensitive tumors, such as squamous cell carcinoma of the head and neck, osteogenic sarcoma, and neuroblastoma, are indicated.

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TABLE 2.—Hematopoietic and renal toxicity tabulated by dose of *cis*-platinum

Dose (mg/m^2)	Lowest recorded counts (× 1000 cells/mm^3)			Day of lowest recorded count	Highest recorded level (mg/100 ml)		Creatinine clearance (ml/min)	
	Platelets	Wbcs	PMN*		BUN	Creatinine	Before treatment	After treatment
75	220	6.1	4.2	20	21	1.6	70	72
100	333	6.8	4.1	10	—	—	47	70
120	201	5.5	3.2	22	22	2.3	72	—
120	135	2.6	1.7	26	20	1.1	160	108
120	171	2.5	0.8	21	14	0.8	80	47
150	209	4.7	1.5	21	35	1.8	70	73
150	189	5.8	1.9	15	45	1.9	73	32
150	128	2.1	0.80	21	30	1.8	108	104
150	164	2.0	0.32	20	45	1.7	47	—

*PMN = polymorphonuclear neutrophils.

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Failure of Carnitine to Prevent Adriamycin Cardiomyopathy [1,2,3]

The major drawback to the clinical utility of Adriamycin is the cumulative dose-related cardiotoxicity. Efforts to prevent or ameliorate the cardiomyopathy have thus far been unsuccessful. Carnitine (γ-trimethyl-ammonium-β-hydroxybutyrate) is a naturally occurring quaternary ammonium compound found in relatively high concentrations in cardiac and skeletal muscle. Its physiologic role is that of a cofactor in fatty acid oxidation. Specifically, it combines with fatty acid acyl-coenzyme A in the presence of carnitine palmityl acyltransferase on the surface of the mitochondrial membrane to form fatty acylcarnitine which readily diffuses into the mitochondria. Once inside, the reaction is reversed, reforming fatty acyl-coenzyme A which then goes on to β-oxidation and resultant energy production (1).

In the course of investigating the cardiac effects of carnitine, Vick et al [4] demonstrated in isolated dog heart (Langendorff) preparations that carnitine pretreatment could prevent acute arrhythmias otherwise produced by coronary artery perfusion with Adriamycin or daunorubicin. Furthermore, carnitine prevented the Adriamycin-induced reduction-in-force of contraction and elevated coronary perfusion pressures seen in the control preparations. Similar effects were observed in intact monkeys given Adriamycin with and without carnitine. In view of these findings, we investigated the effect of carnitine in the rabbit model for Adriamycin cardiotoxicity which demonstrates a cardiomyopathy virtually identical to that seen in man after repeated administration of Adriamycin or daunorubicin (2).

MATERIALS AND METHODS

Four sets of New Zealand white (NZW) rabbits (Vrana's Rabbit Farm, Milville, NJ) weighing 1.6–3.2 kg were treated as follows: (*a*) Adriamycin control—1.1 mg/kg (12.1 mg/m^2) of Adriamycin given iv twice weekly (Days 1 and 3). (*b*) Adriamycin plus carnitine—Adriamycin given twice weekly as above plus carnitine (180 mg/kg iv) given twice on Day 1 (approximately 3–4 hours before and again immediately prior to Adriamycin administration) and daily thereafter for 3 more days (total, five doses per week), with the dose on Day 3 given immediately prior to Adriamycin. (*c*) Carnitine control—carnitine (180 mg/kg iv) given daily for five doses per week. (*d*) Saline control—normal saline given iv twice weekly (Days 1 and 3).

The therapeutic dose of carnitine in the dog and monkey as described by Vick et al [4] is in the range of 1.0–1.2 g/m^2. Because carnitine is a relatively nontoxic drug, with an LD50 in dogs of 7 g/kg (140 g/m^2), [5] a higher therapeutic dose of carnitine at 180 mg/kg (2 g/m^2) was selected for the rabbits to ensure adequate drug exposure. Adriamycin was given at a concentration of 2 mg/ml by slow iv push into a marginal ear vein. The original preparation of carnitine was diluted 1:1 with sterile water for injec-

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[2]We are indebted to Frank Elias, Richard Ashley, and Chaudhry Din for their skilled technical assistance.

[3]Adriamycin (batch No. 192) was generously supplied as the clinical formulation by Dr. Luigi Lenaz of Adria Laboratories, Wilmington, Del. Carnitine (lot No. 837–673) was generously provided by Dr. S. DeFelice, Bio-Basics International, New York, NY.

[4]Vick JA, DeFelice S, Sanzari N, et al. Prevention of Adriamycin induced cardiac toxicity with carnitine. Submitted for publication.

[5]Drug brochure: carnitine. Courtesy of Dr. S. DeFelice, Bio-Basics International, New York, NY.

tion, to minimize phlebitis, and injected by slow iv push at a concentration of 50 mg/ml.

At an average cumulative Adriamycin dose of 204 mg/m² (table 1) the animals were anesthetized with pentobarbital sodium and the hearts were removed while still beating (rabbits 7 and 8 died spontaneously).

Heart muscle (left ventricular free wall and septum) and kidney (cortex and medulla) were prepared for electron-microscopic examination with fixation in either 3.0% phosphate buffered gluteraldehyde solution followed by 1.0% phosphate buffered osmic acid solution at pH 7.2, or the latter solution alone for 2 hours. The blocks were embedded in Epon and ultrathin (600–800 Å) sections were cut with an LKB ultramicrotome, stained with uranyl acetate and lead, and examined under a Siemens 101 electron microscope. Major organs including the heart were also fixed in 10% neutral formalin and 4-μ sections were stained with hematoxylin and eosin, periodic acid-Schiff, and van Gieson's stains.

RESULTS AND DISCUSSION

Table 1 shows the results of the experiment. Rabbits 1–3, who received Adriamycin alone, showed varying degrees of mild to moderate cardiotoxicity appropriate for the relatively low cumulative dose of Adriamycin given. Five rabbits (Nos. 4–8) received Adriamycin plus carnitine. One rabbit (No. 7) died early with septic changes in the spleen and had no cardiac findings. The remaining four animals showed moderate to severe evidence of cardiomyopathy. Animal 5 had cardiomegaly, bilateral pleural effusions, and ascites at the time of death, and rabbit 8 had cardiomegaly and pleural effusions. The carnitine-alone animals (rabbits 9–12) and saline controls (rabbits 13 and 14) had no

TABLE 1.—Results of treatment

Rabbit No.	Drug(s)	Cumulative dose (in mg/m² for Adriamycin and g/m² for carnitine)	Duration of treatment (days)	Cardiomyopathy	Degree of cardiomyopathy*	
					Qualitative	Quantitative
1	Adriamycin	206	70	Present	2+	3+
2	Adriamycin	194	90	Present	1+	1+
3	Adriamycin	206	105	Present	1+	1+
4	Adriamycin + carnitine	206 79	69	Present	2+	2+
5	Adriamycin + carnitine	206 85	89	Present	3+	4+
6	Adriamycin + carnitine	193 85	90	Present	3+	4+
7	Adriamycin + carnitine	85 37	29	Absent†,‡	—	—
8	Adriamycin + carnitine	218 91	75	Present†	3+	4+
9	Carnitine	85	73	Absent	—	—
10	Carnitine	81	89	Absent§	—	—
11	Carnitine	95	77	Absent	—	—
12	Carnitine	87	79	Absent	—	—
13	Saline	135 ml	90	Absent	—	—
14	Saline	153 ml	107	Absent	—	—

*Criteria of Jaenke (3). Qualitative: 1+ = vacuolization of myocardial cells; 2+ = advanced cellular degeneration with loss of myofilaments and homogenization of sarcoplasm; 3+ = connective tissue proliferation and fiber atrophy; 4+ = myolysis and fibroplasia. Quantitative: 1+ = involvement of single scattered myofibers at ≥ 1 level; 2+ = involvement of focal groups of cells at 1 level; 3+ = focal groups at ≥ 2 levels; 4+ = confluent areas of involvement.

†Died spontaneously.

‡Early death, septic spleen (?), no cardiac changes.

§Inadvertently received a single dose of Adriamycin at 12.1 mg/m².

evidence of cardiomyopathy. Over the course of the experiment the average weight gain for the four groups of animals was: Adriamycin alone, 38%; Adriamycin plus carnitine, 9% (excluding No. 7, early death); carnitine alone, 59%; and saline control, 58%.

Histologically, the cardiac changes observed were comparable to those described by Jaenke (2,3) and ranged from vacuolization of myocardial cells to homogenization of sarcoplasm with loss of myofibrils to cellular atrophy with fibroblastic infiltration and early collagen proliferation. Early changes seen in rabbits treated with Adriamycin alone were quite focal in nature; involvement of larger areas of the myocardium at several levels was seen in the double-treated animals. Ultrastructurally, extensive dilation was seen in both sarcoplasmic reticulum and T tubules of double-treated animals (Nos. 4–8). Gluteraldehyde-fixed tissue showed artifactual mitochondrial alterations not observed in osmic acid-fixed sections.

Characteristic pathologic alterations were also noted in the kidneys of animals treated with either Adriamycin alone or Adriamycin plus carnitine. The renal changes consisted of glomerular cell vacuolization, marked tubular atrophy, hyaline cast formation, and focal interstitial fibrosis. Electron-microscopically, the vacuolization was seen in the cytoplasm of podocytes. Saline and carnitine controls had none of these abnormalities. It is speculative whether cardiac, renal, or combined effects were the cause of the effusions noted in two double-treated animals.

Carnitine was investigated as a potential prophylactic agent in the prevention of Adriamycin-induced cardiomyopathy, based on the observations of Vick et al.[6] While Adriamycin has a twofold pattern of cardiac toxicity, ie, acute electrophysiologic effects and delayed cardiomyopathy, the prime clinical drawback in man is the cumulative dose-related cardiomyopathy. The rabbit model for chronic Adriamycin cardiotoxicity, as described by Jaenke (2), seems to correlate well with the histopathologic alterations noted in man (4,5). Despite intensive administration of carnitine, we were unable to prevent the development of typical pathologic alterations in the hearts and kidneys of Adriamycin-treated rabbits (6). The rabbit pathology model which measures cumulative toxicity does not correlate with the carnitine effect of preventing acute arrhythmias and cardiac dysfunction in the isolated dog heart or intact monkey. When given at this dose and schedule, carnitine does not prevent Adriamycin-induced cardiomyopathy or nephropathy in the rabbit model system.

[6]*See* footnote 4.

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Proceedings of the Workshop on Cutaneous T-Cell Lymphomas (Mycosis Fungoides and Sézary Syndrome)

Division of Cancer Treatment
National Cancer Institute

October 20 and 21, 1978
Bethesda, Maryland

Introduction to Workshop

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During the last 2 decades encouraging gains have been made in understanding the pathology, immunology, natural history, and treatment of the cutaneous T-cell lymphomas (CTCL), including mycosis fungoides (MF) and the Sézary syndrome (SS). A workshop on CTCL was held at the National Cancer Institute, Bethesda, Md, on October 20 and 21, 1978. The purposes of the workshop were to review and update current knowledge of these disorders and to arrive at a consensus for the application of pathology, staging, and therapy to serve as the basis for future CTCL research.

Historical Perspective (Table 1)

Figure 1 depicts the first and, in fact, only case of MF seen by Jean Louis Alibert, a French baron and physician. Alibert segregated the case in his 1806 atlas and kept it separated from other disorders in his later book on skin diseases. The patient, a man named Lucas, developed a brawny desquamating rash and, somewhat later, small skin tumors. The tumors resembled mushrooms and exuded a purulent liquid which coagulated and dried. Some of the tumors would shrink and even disappear, leaving behind withered and loose skin which Lucas' daughter was said to have patiently cut away with scissors without causing her father the slightest pain. Other tumors would partially erode, leaving ulcers. Lucas was able to work at his duties as an official of the Department of Forestry for 5 years. He eventually lost weight, and after languishing in bed for 7 months, died of "hectic" fever. "Mycosis fungoides" was the name Alibert used for this condition (1).

During the period from 1806 to 1960 investigators were primarily concerned with clinical and pathologic descriptions of the cutaneous manifestations of these disorders. As early as 1868, Gillot (2) concluded that MF was a disorder of lymphoid tissue and was similar to leukemia. Bazin (3), a French dermatologist, described the three classic clinical cutaneous stages of the disease in 1870: (*a*) nonspecific erythematous or premycotic, (*b*) plaque, and (*c*) tumor. In 1885, Vidal and Brocq (4) described a variant of the above clinical patterns, termed the d'emblée variant, in which tumors developed without preceding eczematous or plaque lesions. The erythrodermic variant was described by Besnier and Hallopeau in 1892 (5). In 1938, Sézary and Bouvrain (6) described abnormal hyperchromatic and hyperconvoluted cells in skin and peripheral blood associated with erythroderma. The cytologic description of these cells was further refined by Taswell and Winkelmann in 1961 (7). The ultrastructural appearance of the "Sézary" cell, with the classic highly serpentine convoluted or cerebriform nucleus with condensed heterochromatin at the periphery was described by Lutzner and Jordan in 1968 (8). Similar cells were identified in skin and lymph node biopsies of patients with both SS and MF in the early 1970s (9–13). Small cell and large cell variants of SS were also described during this period (14).

In 1970, Crossen and co-workers (15) made two original observations about the disorders: (*a*) the abnormal cell was lymphocytic in origin and responded to phytohemagglutinin, and (*b*) the cells had abnormal cytogenetics. Shortly thereafter, Brouet et al (16) and Broome et al (17) demonstrated that the abnormal lymphocyte had T-cell properties. The T-cell nature of these cells was soon demonstrated in peripheral blood, skin, and lymph nodes of patients with both MF and SS (18,19). These abnormal T cells are sufficiently differentiated to assume some of the properties of normal T cells, as shown by Broder and co-workers (20). The cytogenetic abnormalities were also confirmed and extended to cells from blood, skin, and lymph nodes of patients with both disorders (14,21–25).

In many early reports, MF was stated to undergo transition to other forms of malignant lymphoma, especially during the later stages of disease when visceral involvement became apparent. In 1974, Long and Mihm (26) and Rappaport and Thomas (27) independently reported that the neoplastic cel-

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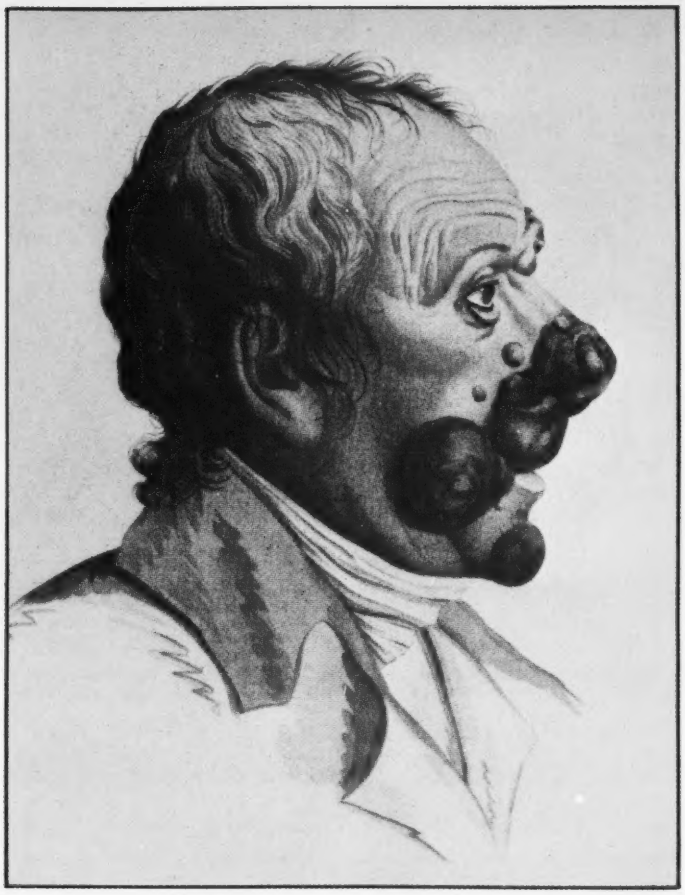

FIGURE 1.—Drawing of first and only case of MF seen by Jean Louis Alibert (1806).

lular proliferation in extracutaneous MF is identical to that in the skin. They felt that extracutaneous dissemination was a distinct aspect of the natural history of MF rather than a precursor of variable types of malignant lymphoma.

Although some still feel that MF is an inflammatory non-neoplastic reticulosis (28,29), by the 1960s most investigators were concerned with the neoplastic potential of the disease. In the 1970s, there has been a general consensus that the disorder is, in fact, a malignant lymphoma with an initial predilection for the skin. The epidemiology and pathogenesis of the disorder are still not well-defined.

During the early 1970s, several institutions reported on the clinical aspects of large series of patients, allowing prognostic variables to be identified. The most important prognostic signs were shown to be the extent and type of cutaneous involvement, the presence or absence of lymphadenopathy, and the presence or absence of visceral involvement (30,31). Sex, age, and absolute lymphocyte count were also reported to have some prognostic importance (30,32). Several different clinical staging classifications were developed on the basis of these variables (31,33–35).

Clinical staging procedures, such as those employed in the routine pretreatment evaluation of patients with Hodgkin's disease and the non-Hodgkin's lymphomas, have not been routinely applied to patients with CTCL. However, reports have appeared on the value of lymphangiography and staging laparotomy (36–38).

During the 1960s and 1970s, at least four major forms of therapy were shown to produce consistent regression of MF lesions: (*a*) topical chemotherapy

TABLE 1.—History of the CTCLs

Yr	Author(s) and ref No.	Finding
1806	Alibert (1)	Original description
1870	Bazin (3)	3 classic cutaneous stages
1885	Vidal and Brocq (4)	D'emblée variant
1892	Bresnier and Hallopeau (5)	Erythrodermic variant
1938	Sézary et al (6)	Leukemic variant with erythroderma
1968	Lutzner and Jordan (8)	Ultrastructural description of Sézary cell
1970	Crossen et al (15)	Lymphocyte properties of abnormal cell
1973	Brouet et al (16) and Broome et al (17)	T-cell nature of abnormal cell
1970–1973	Crossen et al (15) and Lutzner et al (14)	Abnormal cytogenetics
1972–1973	Epstein et al (32) and Fuks et al (30)	Appreciation of prognostic factors
1974	Long and Mihm (26) and Rappaport and Thomas (27)	Description of extracutaneous MF

(33), (*b*) total-body electron-beam radiotherapy (30), (*c*) systemic chemotherapy (39), and (*d*) photochemotherapy (40). The Stanford group has reported that electron-beam radiotherapy may be curative for some patients with limited cutaneous lesions (30). This report has not yet been confirmed and the optimal treatment strategy for each stage has not yet been determined.

Conclusions

Most investigators would agree on the following conclusions based on the above-mentioned findings: (*a*) MF and SS are part of a distinct clinical and pathologic entity for which we will use the term cutaneous T-cell lymphoma. (*b*) The CTCLs are malignant disorders with a wide range of natural history. The malignant nature of these disorders is demonstrated by the shortened lifespan of patients with CTCL, the lack of spontaneous remissions, and the abnormal cytogenetics. (*c*) The abnormal "mycosis" or "Sézary" cell is a T lymphocyte with a characteristic cerebriform appearance. The abnormal cells have the same appearance in skin, lymph node, and blood. While histologic criteria for involvement of skin and viscera are becoming more apparent, controversy persists over criteria for lymph node involvement. (*d*) Extent of disease is the most important prognostic variable. However, routine staging procedures and a uniform staging classification have not been defined. (*e*) While many therapeutic modalities consistently produce regressions of skin lesions, the optimal therapy for each stage has not been determined. (*f*) The "mycosis" or "Sézary" cell often is sufficiently differentiated to perform T-cell functions which may provide a unique opportunity for the study of T-cell biology.

Goals of the Workshop

The goals of the CTCL workshop were twofold. The first was to update recent developments in the study of these disorders. The second was to define, through three separate panels, the application of pathology, staging, and therapy to serve as the basis for future research. The first goal was met through a series of formal reports presented as papers in these proceedings and the second as three consensus reports discussed in-committee and accepted by the attendees in a joint session. The consensus statements appear at the end of this report.

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Ultrastructural Appearance of Cutaneous T Cell Lymphomas in Skin, Lymph Nodes, and Peripheral Blood

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SUMMARY

An ultrastructural analysis of skin and lymph node biopsies and peripheral blood specimens was performed in 39 patients with cutaneous T cell lymphomas (CTCL), including 14 patients with erythroderma and 25 patients with plaques or tumors, and in 21 control patients with benign chronic dermatoses (BCD). These electron-microscopic studies facilitated recognition of atypical convoluted lymphocytes. Single, atypical, moderately convoluted lymphocytes (MDCL) (mycosis cells) were identified in skin and lymph node biopsies from all patients with CTCL and the majority of patients with BCD. Thus, the finding of single MDCL is not useful in distinguishing CTCL from BCD. Clustered MDCL were found in the skin and lymph node biopsies of the majority of CTCL patients. In contrast, clustered MDCL were present in skin biopsies of only four of 16 patients with BCD. No clusters were identified in lymph node biopsies from five patients with BCD. The occurrence of clustered MDCL in skin biopsies of patients with BCD is not understood. It is possible that this finding may indicate the presence of an early CTCL. MDCL were present in the peripheral blood specimens of all patients with CTCL and erythroderma; they were also present in the blood of 11 of 25 patients with plaque- and tumor-stage CTCL, although they occurred rarely in all but two of these patients. The significance of the small numbers of these cells in the blood of CTCL patients is unknown. Atypical markedly convoluted lymphocytes (Sézary cells) were found only in patients with CTCL, but were infrequent. Although these cells have been considered diagnostic of CTCL, they were found in a minority of CTCL patients.

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Two recent advances in the understanding of the cutaneous T cell lymphomas (CTCL) were the recognition of their T cell nature (1,2) and the ultrastructural demonstration of the unique, convoluted, cerebriform nucleus of the neoplastic T cell (3,4). In their ultrastructural study of the Sézary syndrome (SS), Lutzner and Jordan (3) described the characteristic serpentine, cerebriform, ribbon-like nucleus of the Sézary cell. Lutzner et al (4) later observed that the mycosis cell differed from the Sézary cell by having a nucleus which is less infolded, ultrastructurally. In some studies of CTCL, however, a distinction between the convoluted mycosis cell and the more highly convoluted Sézary cell was not made (5,6). Clusters of atypical convoluted cells have been described in an ultrastructural study of skin and lymph nodes from patients with mycosis fungoides (MF), but not from controls (7).

Lymphocytes closely resembling mycosis and Sé-

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zary cells have been noted in specimens from normal individuals and from patients with benign diseases. The specimens included normal human cord blood and normal peripheral blood (8), normal lymphocytes obtained from normal peripheral blood and stimulated with phytohemagglutinin in tissue culture (9), normal skin biopsies maintained in organ culture (10), skin biopsies from patients with a wide variety of benign skin conditions (11,12), and lymph node biopsies showing reactive lymphadenitis and obtained from patients who did not have MF (7). A variety of terms have been applied to these cells, including Sézary-like cell (9,10), MF-like cell (13), cerebriform-mononuclear cell (8), and convoluted lymphocyte (12). This variation in terminology has further complicated the problem of the exact significance of these cells in biopsy specimens from patients with both benign and malignant diseases.

The purpose of this ultrastructural study was to define the two variants of atypical convoluted lymphocytes in CTCL (ie, mycosis cell and Sézary cell) and to determine their relative incidence in skin and lymph node biopsies and peripheral blood specimens of patients with CTCL. Skin, lymph node, and peripheral blood specimens from patients with benign chronic dermatoses (BCD) were used as controls.

MATERIALS AND METHODS

Specimens of skin, enlarged peripheral lymph nodes, and buffy coats of peripheral blood were obtained from 39 patients with CTCL, including 25 patients with plaques or tumors (MF) and 14 with generalized erythroderma (SS). Skin and lymph node biopsies from 21 patients with BCD of at least 6 months' duration were also studied (table 1). Skin and lymph node biopsies were fixed for electron microscopy in 2.5% glutaraldehyde at pH 7.4 and postfixed with Veronal buffered osmium tetroxide. Dehydration in graded ethanols was followed by embedding in Epon 812. Peripheral blood specimens were collected in Vacutainer tubes containing heparin and centrifuged for 20 minutes at 1000 rpm. The supernatant plasma was replaced by 2.5% glutaraldehyde and the specimen was stored for 4 hours at 4°C. The firm buffy coat was then minced in 1-mm cubes, fixed for an additional 2–20 hours in 2.5% glutaraldehyde, and processed as above. Sections 1-μ thick were prepared using glass knives and an LKB ultratome III. They were stained with toluidine blue for selection of fields with the light microscope. Ultrathin sections were prepared using diamond knives and the LKB ultratome III, stained with uranyl acetate and lead citrate, and examined and photographed in an AEI–801 electron microscope. In all cases, hematoxylin and eosin-stained sections of the skin and lymph node biopsies and Wright-Giemsa-stained peripheral blood smears were available for review and comparison.

TABLE 1.—Diagnosis for patients with BCD

Diagnosis	No. of patients
Psoriasiform dermatitis	3
Atopic dermatitis	2
Alopecia mucinosa	2
Lichen planus	2
Porphyria	2
Eczema	2
Exfoliative dermatitis	1
Chronic folliculitis	1
Drug-induced lupus erythematosus	1
Erythema annulare centrifugum	1
Atypical pityriasis rosea	1
Neurodermatitis	1
Nummular eczema	1
Mucha-Habermann's disease	1

DEFINITIONS

Abnormal convoluted lymphocytes similar to the mycosis cells described and illustrated by Lutzner et al (4) were characterized by their moderately convoluted nuclei. The nuclei of these cells had at least one deep indentation of the nuclear envelope which extended to at least the center of the nucleus. Several more shallow nuclear envelope indentations were also present (fig 1). Because of the variation in the terminology applied to these cells in previously published ultrastructural studies, we prefer a descriptive term for these cells, ie, moderately convoluted lymphocytes (MDCL). Abnormal convoluted lymphocytes similar to the large Sézary cells described and illustrated by Lutzner and Jordan (3) were characterized by their markedly convoluted nuclei. Ultrastructurally, these cells had thin, ribbon-like nuclei which were folded upon themselves three to five times (fig 2). Because of the variation in the terminology applied to these cells, we prefer a descriptive term for them, ie, markedly convoluted lymphocytes (MKCL).

In our ultrastructural study of the skin and lymph node biopsies, we frequently encountered clustered abnormal convoluted lymphocytes in the cellular infiltrates. A "cluster" is defined as at least three closely opposed MDCL and/or MKCL (fig 3).

SKIN BIOPSIES

Single scattered MDCL were noted in cellular dermal infiltrates in skin biopsies from 14 of 16 patients who had BCD and from all of the 39

TABLE 2.—Ultrastructure of skin and lymph node biopsies

	No. of biopsies with—		
	Single MDCL	Clustered MDCL	MKCL
	Skin biopsies		
BCD (total: 16 patients)	14	4	0
MF (total: 25 patients)	25	25	3
SS (total: 8 patients)	8	7	3
	Lymph node biopsies		
BCD (total: 5 patients)	4	0	0
MF (total: 15 patients)	15	10	2
SS (total: 12 patients)	12	11	4

patients who had CTCL (table 2). Clustered MDCL were not observed in the skin biopsies from 12 of 16 patients with BCD. In the remaining four patients with BCD, two with psoriasiform dermatitis and two with atopic dermatitis, clustered MDCL were noted ultrastructurally in the skin biopsies, but were not appreciated on initial light-microscopic interpretation of the skin biopsies. One of the four patients with BCD and clustered MDCL subsequently developed MF. No MKCL were identified in the skin biopsies of these 16 patients.

Clustered MDCL were present in the skin biopsies

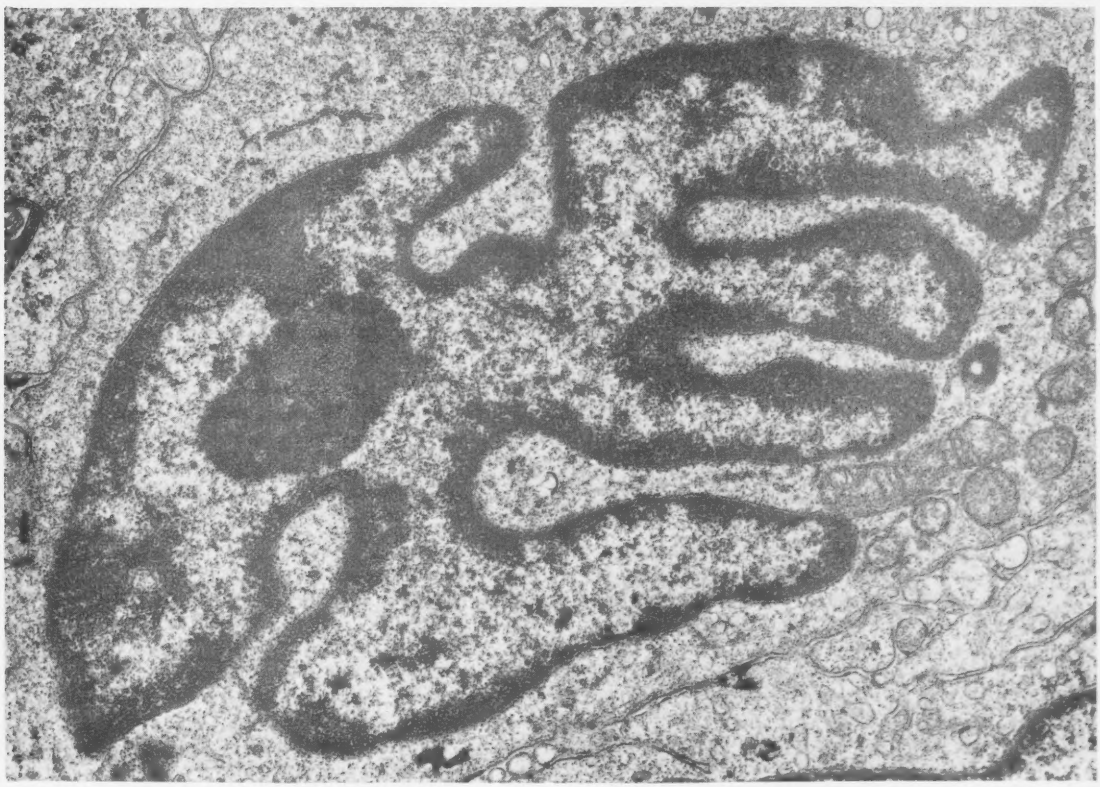

FIGURE 1.—MDCL (uranyl acetate and lead citrate stain, × 6300).

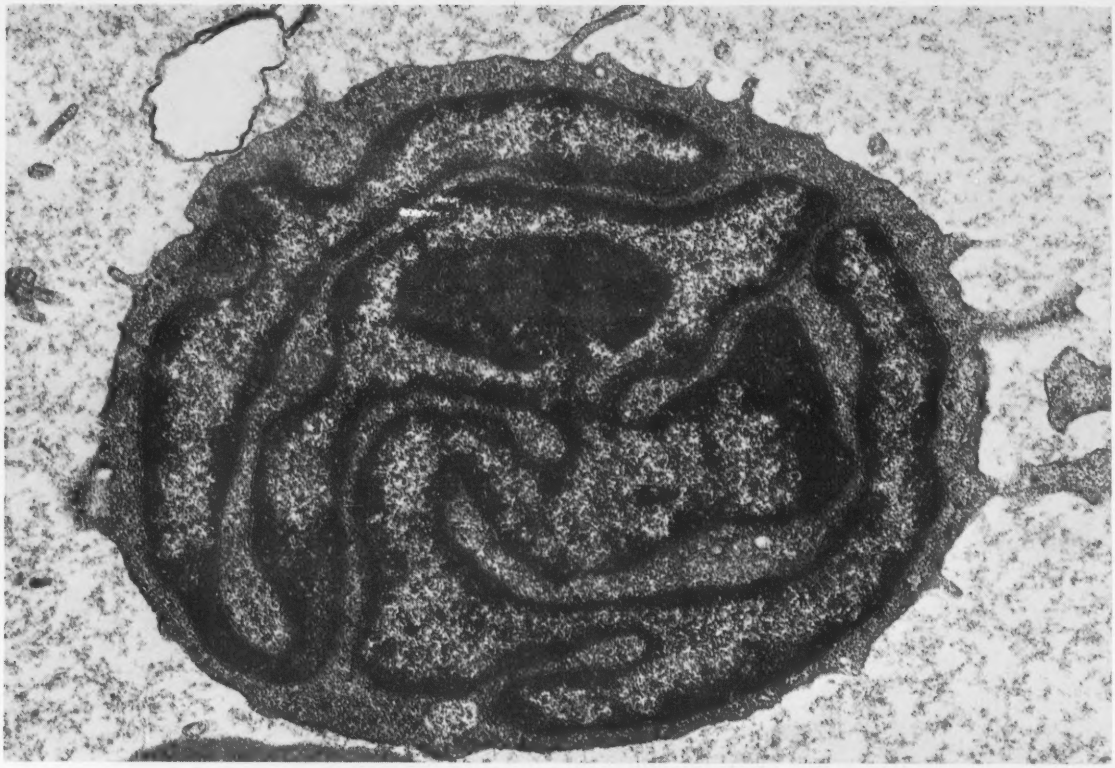

FIGURE 2.—MKCL (uranyl acetate and lead citrate stain, × 6300).

from all 25 patients with MF and in seven of eight with SS. Occasional single MDCL and no MKCL were noted in the sparse cellular dermal infiltrate present in the skin biopsy from the eighth patient who had SS. Single MKCL were present in skin biopsies from three of 25 patients with MF and three of eight with SS.

LYMPH NODE BIOPSIES

Occasional single MDCL were noted in lymph node biopsies from four of five patients with BCD (table 2). MKCL and clustered MDCL were not noted in any of the lymph node biopsies from five patients with BCD. On light microscopy, changes of dermatopathic lymphadenitis were also present in four of these five lymph node biopsies. Reactive lymphadenitis was present in the fifth lymph node biopsy.

Single MDCL were present in the lymph node biopsies from all of the 27 patients who had CTCL. In contrast to the patients with BCD, clustered MDCL were present in lymph node biopsies from ten of 15 patients with MF and from 11 of 12 with SS. On light microscopy, changes of dermatopathic lymphadenitis were present in lymph node biopsies from all patients with MF and from nine of 12 with SS. In one of the 12 SS patients, the lymph nodes contained a diffuse infiltrate of malignant lymphoblasts and no MDCL were identified, ultrastructurally. Lymph nodes from the remaining two patients with SS contained a diffuse lymphomatous infiltrate with clustered MDCL.

MKCL were noted in the lymph node biopsies from two of 15 patients with MF and from four of 12 with SS.

PERIPHERAL BLOOD

MDCL were rarely observed in buffy coats of peripheral blood from two patients with BCD (table 3). MKCL were not identified.

MDCL were rarely identified in the buffy coats of peripheral blood of nine patients with MF; in five of these patients, abnormal convoluted lymphocytes were not appreciated in the light-microscopic study

TABLE 3.—Ultrastructure of peripheral blood specimens

	No. of specimens with—	
	MDCL	MKCL
BCD (total: 2 patients)	0	0
MF (total: 25 patients)	11	1
SS (total: 14 patients)	14	10

of peripheral blood smears. In two additional patients with MF, MDCL were present in appreciable numbers in the buffy coats. MDCL were not observed in buffy coats from the remaining 14 patients with MF. MDCL were present in the buffy coats from all of the 14 patients with SS. These MDCL were the predominant abnormal lymphocytes in the peripheral blood of the 14 patients with SS. Rare-to-occasional MKCL were present in buffy coats from one of 25 patients who had MF and from ten of 14 who had SS.

DISCUSSION

In our ultrastructural study of skin and lymph node biopsies and peripheral blood specimens, the electron microscope facilitated recognition of MDCL and MKCL. It was especially useful when these cells were difficult to appreciate in the light-microscopic study of biopsy specimens and peripheral blood smears. The abnormal convoluted lymphocytes may be missed by light microscopy in thick and/or overstained sections. Clustered MDCL were not appreciated during the initial study of hematoxylin and eosin-stained sections of the skin biopsies from four patients who had BCD. These cells were readily apparent on ultrastructural study of the biopsies. These cells may also be missed at the light-microscopic level when they are few in number. In five patients who had MF and negative peripheral blood smears, ultrastructural study revealed the presence of rare-to-occasional MDCL in the buffy coats. Although 1-μ thick sections of the biopsy

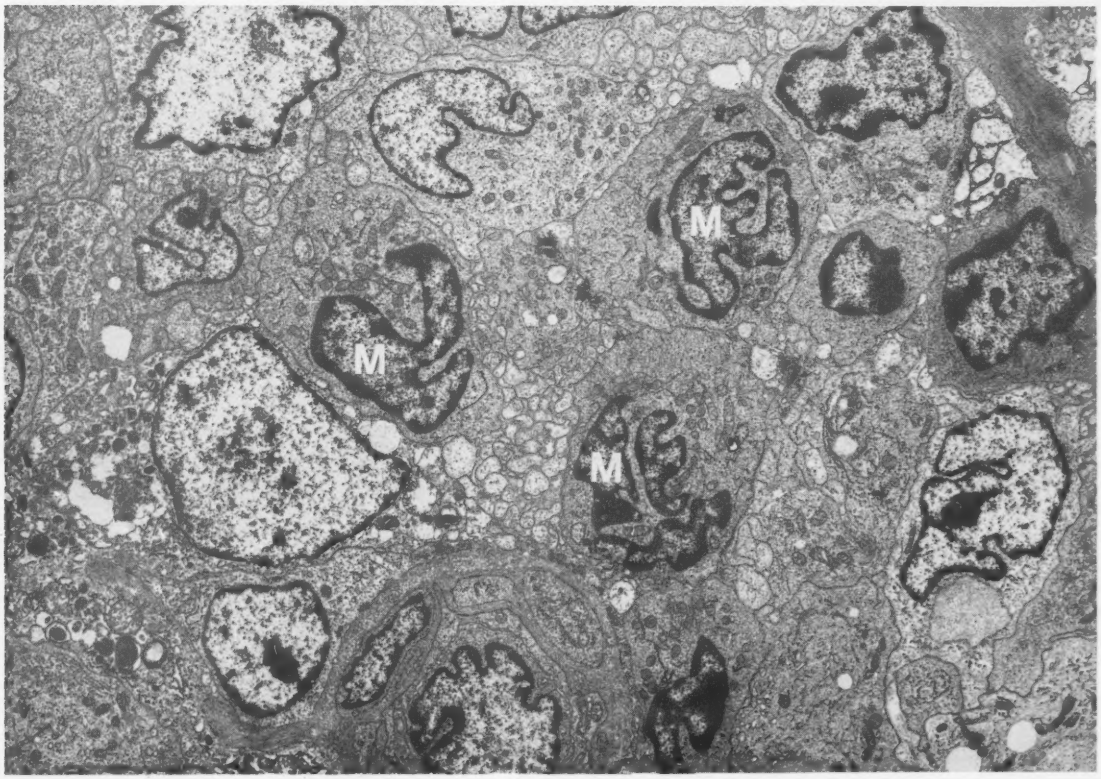

FIGURE 3.—Cluster of 3 MDCL (M) in lymph nodes from SS patient (uranyl acetate and lead citrate stain, × 1600).

specimens and buffy coats also facilitated recognition of MDCL, differentiation of these cells from convoluted histiocytes was frequently difficult. The electron microscope permitted easy distinction of these cells.

Scattered single MDCL were frequently noted in skin and lymph node biopsies from patients who had BCD and CTCL and this finding was considered to be nonspecific. Clustered MDCL were not observed in skin biopsies from 12 of 16 patients with BCD. In contrast, they were found in skin biopsies from 32 of 33 patients with CTCL. Thus, the presence of clustered MDCL in skin biopsies is considered highly suggestive of CTCL. One of the four patients with BCD and clustered MDCL subsequently developed MF. The other three patients are being closely followed for the possible development of overt clinical CTCL. The electron microscope may be a helpful tool to identify those patients who have previously undetected premycotic skin disease and who may subsequently develop CTCL.

Clustered MDCL were frequently noted in lymph node biopsies from 21 of 27 patients with CTCL, whereas they were not found in the lymph node biopsies from five patients with BCD. Thus, the occurrence of clustered MDCL in lymph node biopsies is considered highly suggestive of involvement of the lymph node by CTCL. Clustered MDCL were noted in the lymph node biopsies from ten of 15 MF patients. The exact significance of these data is unclear and must await correlation with the course of the patients' diseases and their response to therapy. Clustered MDCL were associated with changes of dermatopathic lymphadenitis in 19 of 27 lymph node biopsies from patients with CTCL. In some of these cases appreciation of the presence of clustered MDCL in the dense infiltrate of dermatopathic lymphadenitis was difficult on initial study of the hematoxylin and eosin-stained sections and ultrastructural study facilitated recognition of clustered MDCL.

Rare-to-occasional MDCL were noted in the ultrastructural preparations of buffy coats from 11 of 25 MF patients. The exact significance of this finding is not apparent and must await correlation with the clinical course of the patients. In this study, MDCL were found to be the predominant abnormal lymphocytes in the peripheral blood of patients with erythroderma, including those with lymphocytosis (SS). Many of the cases in the present study may correspond to the small cell variant of SS described by Edelson et al (14).

MKCL were sparsely found in biopsy specimens and buffy coats of patients with CTCL but not in patients with BCD. Thus, although MKCL may be markers for CTCL, they were not the predominant abnormal lymphocytes in patients with this disease in this study. MKCL closely resemble the large cell variant of the Sézary cell as described and illustrated by Edelson et al (14). In some SS cases described by this group, the large Sézary cell was the predominant abnormal lymphocyte in the peripheral blood.

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Blood and Lymph Node T Lymphocytes in Cutaneous T Cell Lymphoma: Evaluation by Light Microscopy [1]

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SUMMARY

Cytology of peripheral blood and lymph node lymphocytes from a group of unselected patients with cutaneous T cell lymphoma (CTCL) was studied by light microscopy. Twenty of 45 patients had circulating lymphocytes with convoluted nuclei recognized in routine Wright-Giemsa-stained peripheral blood smears. Cytocentrifuge preparations of E-rosetted lymphocytes showed that > 10% of the T cells had convoluted nuclei in each of 16 patients with positive blood smears and in six of 17 whose blood smears were negative or inconclusive. Peripheral blood involvement with > 10% convoluted T cells was most frequent in patients with erythroderma (100%) including those with normal or decreased lymphocyte counts, and was not uncommon in patients with mycosis fungoides in the plaque or tumor phase (42%). The light-microscopic morphology of the abnormal cells found in the patients with the plaque or tumor phase of mycosis fungoides was not distinguishable from that of the erythrodermic patients. Increased percentages (> 15%) of T cells having convoluted nuclei were also found in the lymph node cell suspensions from CTCL patients with adenopathy (18 of 25 patients). These results suggest that a high frequency of extracutaneous involvement occurs in patients with CTCL, the clinical significance of which remains to be determined.

[Cancer Treat Rep 63:571–574, 1979]

A major advance in understanding the relationship of mycosis fungoides (MF) to the Sézary syndrome came with the discovery that the morphologically bizarre lymphoid cell associated with both conditions has the surface membrane characteristics of the T lymphocyte (1–3). This discovery has led to the unifying, although somewhat controversial, concept that these two conditions are part of a spectrum of dermatologic malignancies termed the cutaneous T cell lymphomas (CTCL) (4). We have used the ability to recognize T cells by their ability to rosette with sheep rbcs to increase the specificity of light-microscopic evaluation of peripheral blood and lymph node lymphocytes in patients with CTCL. Our results suggest that there is a high frequency of peripheral blood and lymph node involvement in these patients.

METHODS

Subjects.—Forty-five patients with histologically confirmed CTCL including 18 with erythroderma and 27 with the plaque or tumor phase of MF were studied. Seven patients with chronic benign skin disease served as part of a group of non-CTCL controls; the remaining non-CTCL controls were

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healthy hospital employees or patients from the hematology or oncology clinics who did not have skin disease.

Methods.—Wright-Giemsa-stained peripheral blood smears from the 45 CTCL patients were combined with the smears from 14 non-CTCL patients and evaluated without knowledge of the clinical diagnosis. In 33 CTCL patients and in ten non-CTCL patients, mononuclear cells were isolated from the peripheral blood by Hypaque-Ficoll centrifugation and incubated with sheep rbcs (5) or AET-treated sheep rbcs (6) to allow T lymphocytes to become rosetted. Cytocentrifuge preparations of the E-rosetted mononuclear cell suspensions were stained with Wright-Giemsa and evaluated by light microscopy (× 1500). The nuclear morphology of at least 50 lymphocytes in the routine peripheral blood smear and 200 rosetted lymphocytes in the cytocentrifuge preparation was examined. Cells were considered convoluted if the nuclei were folded, deeply indented, grooved, or angulated (figs 1 and 2). Twenty-five CTCL patients with adenopathy had a lymph node biopsy. A suspension of lymph node cells was prepared by mincing a portion of the node in TC 199 (GIBCO, Grand Island, NY). The cells were then rosetted with sheep rbcs using the same method used with the peripheral blood mononuclear cells.

RESULTS

In the blinded study of the routine peripheral blood smears, 20 of 45 CTCL patients were considered to have lymphocytes with sufficiently bizarre morphology to be diagnostic of peripheral blood involvement by CTCL (Sézary) cells. Generally, more than one third of the lymphocytes in these patients' blood smears had some nuclear abnormality. The absolute lymphocyte count in the patients with positive cytology ranged from 870 to 133,000/μl (median, 4800/μl).

There were a wide variety of abnormalities, ranging from small grooved cells to large, highly convoluted, hyperchromatic cells, occurring within the same patient and among different patients (fig 1). In one half of the patients the lymphocytes were small (7–10 μ), highly grooved cells consistent with the small cell variant of CTCL previously described by Lutzner et al (7).

Erythroderma was the most common skin lesion associated with peripheral blood involvement recognized by routine light microscopy. Two patients, one with the generalized plaque phase and the other with the tumor phase of MF, also had circulating abnormal lymphoid cells indistinguishable from those of the erythrodermic patients (table 1). Eight other patients with either the plaque or tumor

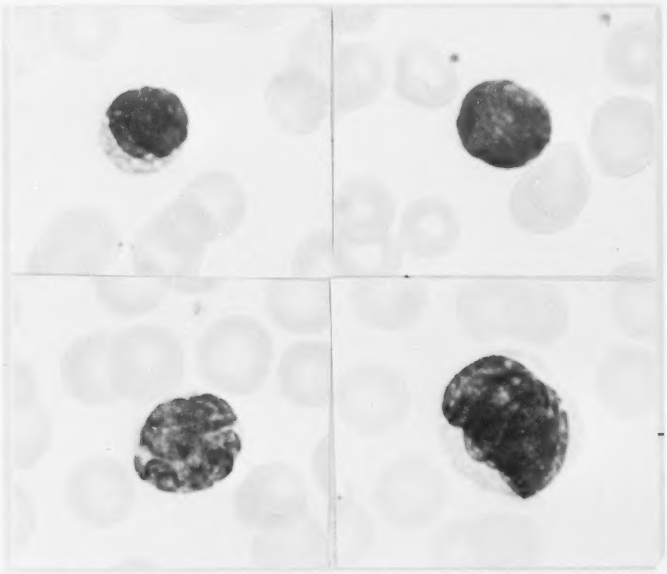

FIGURE 1.—Convoluted lymphocytes in peripheral blood smears of CTCL patients. Cells in top photomicrographs are examples of small cell variant; 2 cells in the lower panel are from a patient with large and small convoluted cells (mixed cell type).

TABLE 1.—Cytology of peripheral blood lymphocytes in CTCL

	Routine smear*		Convoluted T cells	
	Positive	Suspect	> 15%	10%–15%
CTCL patients				
Erythroderma	18/18†	0/18†	14/14‡	0/14‡
Plaques or tumors	2/27	8/27	3/19	5/19
Non-CTCL controls§	0/14	4/14¶	0/10	0/10

*Read without knowledge of the diagnosis.

†Values = No. of patients with peripheral blood involvement/total No. of patients evaluated.

‡Values = No. of patients with > 15% or 10%–15% T lymphocytes with convoluted nuclei in cytocentrifuge preparations of peripheral blood mononuclear cells/No. of patients evaluated.

§Includes 6 patients with chronic skin conditions; remaining patients were randomly selected from our hematology and oncology clinics.

¶Chronic dermatitis, 1 patient; nodular lymphoma, 1 patient; and lymphopenia associated with non-hematologic malignancies, 2 patients.

phase of MF had peripheral blood smears which were considered suspect for peripheral blood involvement but inconclusive. However, blood smears in four of 14 non-CTCL patients were also considered to be suspect. Most of the patients with blood smears considered to be suspect were either moderately or severely lymphopenic.

The morphology of E-rosetted lymphocytes (T cells) was evaluated in 33 patients. Sixteen patients who had "positive" peripheral blood smears had a range of 18%–72% convoluted T cells (median, 37%). Figure 2 illustrates a rosetted convoluted lymphoid cell. Six MF patients whose peripheral blood smears were considered suspect (four patients) or negative (two patients) had between 10% and 20% convoluted cells (median, 14%). All of the control subjects (six patients with chronic skin disease and four healthy controls) had < 10% convoluted cells.

Twenty-five patients had biopsies of enlarged lymph nodes and cytologic evaluation of E-rosetted lymph node cells. In 18 of the 25 patients there were > 15% convoluted T cells with a median of 24% (range, 16%–57%). The remaining seven patients did not differ from the six non-CTCL patients (reactive lymphadenitis, three; dermatopathic lymphadenitis, one; lymphomatoid papulosis, one; and sarcoid, one); they had a median of 8% convoluted T lymphocytes (range, 5%–14%).

DISCUSSION

In the present study we have found that careful examination of a large number of lymphocytes (at least 50) in well-prepared blood smears revealed a high frequency of peripheral blood involvement in CTCL patients, particularly in those with erythroderma. The predominant abnormal lymphocytes in one half of the patients with positive smears were

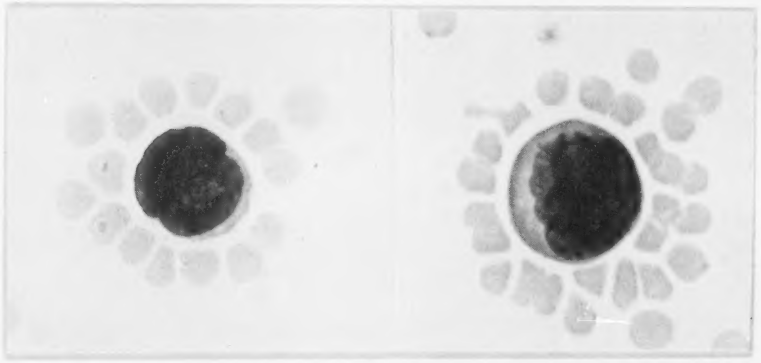

FIGURE 2.—E-rosetted convoluted lymphocytes from peripheral blood of 2 patients with CTCL.

similar to the small cell variant of Lutzner et al (7). Nevertheless, the highly grooved nuclei of these cells allowed them to be readily distinguished from normal lymphocytes and chronic lymphocytic leukemia lymphocytes by light microscopy, particularly when the cells were found in normal or high concentrations (> 2500/μl). Confirmation of the T cell nature of the abnormal lymphocytes by the E-rosetted cytocentrifuge preparations corroborated the diagnosis from the blood smear as did the ultrastructural studies reported by Guccion et al at this meeting (8) which were evaluated independently.

On the other hand, peripheral blood involvement by CTCL cells in patients with lymphopenia was more difficult to recognize by using the routine peripheral blood smear alone. In the blinded study reported here a moderate number of patients with the plaque or tumor phase of MF had "suspect" or "inconclusive" blood smears. Since a similar percentage of the non-CTCL control group was also placed in this category, due to a high degree of suspicion for the small cell variant, there appeared to be a high risk for error in the "suspect" category when applied to lymphopenic patients.

Evaluation of the morphology of E-rosetted lymphocytes eliminated possible confusion by abnormal B lymphocytes and monocytes and thereby increased specificity. Patients with positive blood smears had high percentages of convoluted T lymphocytes. More importantly, six of 17 CTCL patients whose smears were considered inconclusive or negative had similar convoluted E-rosetted lymphocytes of intermediate percentages (10%–20%), while all of the controls had 10% convoluted cells.

Use of the T cell marker also led to the recognition of convoluted T lymphocytes in the lymph nodes of patients with adenopathy more frequently than previously reported. The ultrastructural studies by Guccion et al (8) on the blood and lymph nodes from most of the same patients showed very good correlation and corroborated the light-microscopic findings in most cases. Similar increased frequencies of blood and lymph node involvement in MF have also been previously reported at the ultrastructural level (9,10). At this meeting, Moran et al (11) also reported a comparable incidence of blood involvement recognized at the light-microscopic level in MF patients. Moreover, in their series, the peripheral blood infiltration recognized had prognostic importance. The high frequency of extracutaneous involvement found in these series may therefore represent significant invasion by malignant cells. Alternatively, it may reflect a small fraction of abnormal T cells from the skin (or possibly another site of origin such as lymph nodes) which recirculate in the manner of normal T cells.

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Cytogenetic Abnormalities in Patients With Cutaneous T-Cell Lymphomas

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SUMMARY

Cytogenetic studies were conducted in 36 patients with histologically confirmed cutaneous T-cell lymphomas at the National Cancer Institute-Veterans' Administration Medical Oncology Branch. Aneuploidy was observed in 17 (85%) of the 20 lymph nodes, 23 of the 36 peripheral bloods, and five of the 31 bone marrows. Aneuploidy was frequently present even when tumor cells were not noted histologically. These findings indicate that cytogenetic studies can be very useful for the early detection of malignant cells even when only a few such neoplastic cells are encountered. In this study, the cytogenetic abnormalities found to be characteristic of the disease included extensive aneuploidy, with both numerical and structural aberrations, a wide range of heteroploidy, and a lack of clone formation until the terminal phase of the disease. The numerical changes most frequently involved chromosomes 8, 15, 11, 17, 21, and 10, and the chromosome most involved in structural aberrations was chromosome 1, followed by chromosomes 7, 14, 16, 6, and 9. Cytogenetic studies demonstrate that neoplasia in the cutaneous T-cell lymphomas commonly involves areas beyond the skin.

[Cancer Treat Rep 63:575–580, 1979]

There have been very little cytogenetic data reported for the cutaneous T-cell lymphomas (CTCL), including mycosis fungoides and the Sézary syndrome (1–5). Chromosome banding studies have been published in only one instance, a case of Sézary syndrome reported by Dewald et al (2). The limited amount of data is due to several factors including the low incidence of these diseases, the poor response of the neoplastic T cells to in vitro culture systems, and the technical difficulties encountered in making adequate chromosome preparations. Nevertheless, it is possible to demonstrate some characteristic cytogenetic findings in these diseases and the majority of patients show heteroploidy, multiple markers (including minute and ring chromosomes), and lack of modality and clone formation.

Studies have also been complicated by the difficulty in detecting these neoplastic cells beyond the skin lesions, especially when few such cells are present. The present study demonstrates that cytogenetics can be an effective tool in the early detection of neoplastic cells in the peripheral blood and lymph nodes of patients with CTCL.

MATERIALS AND METHODS

Samples of peripheral blood, bone marrow, lymph node, and/or skin tumor were collected from 36 patients with histologically confirmed CTCL treated at the National Cancer Institute-Veterans' Administration Medical Oncology Branch. The skin disease was characterized by limited plaques in three patients, generalized plaques in 13 patients, tumors in six patients, and erythroderma in 14 patients. Five patients with generalized plaques or erythroderma had received prior systemic chemotherapy. The

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TABLE 1.—Cytogenetic results in peripheral blood

Peripheral blood smear	No. of samples	Cytogenetic results*			
		+	±	–	NM
Positive					
Plaques or tumors	2	0	0	2	0
Erythroderma	14	11	1	1	1
Negative					
Plaques or tumors	20	6	4	6	4

*+ = presence of aneuploidy; – = absence of aneuploidy; ± = patients with only 1 or 2 aneuploid cells; NM = no mitoses.

remaining 31 patients had never received systemic therapy for their disease. For the cytogenetic studies, peripheral blood, lymph node, and skin tumor cell suspensions were cultured for 1, 2, or 3, and 5–7 days with or without phytohemagglutinin stimulation (6). Bone marrow samples were processed directly (without culture) according to the method of Tjio and Whang (7). Lymph node biopsies were obtained from all patients with clinical lymphadenopathy. Blind lymph node biopsies were not obtained from patients without adenopathy.

Chromosome banding techniques (8) were applied to one half of the available slides and the resulting cells were karyotyped according to the rules established by the Paris Conference (9). When possible, 30 cells were analyzed from each specimen. Tables 1–3 show the presence or absence of aneuploidy, whether due to numerical aberrations or chromosomal rearrangements.

An additional four patients, one each with parapsoriasis, lymphomatoid granulomatosis, alopecia mucinosa, and lymphomatoid papulosis, had relatively benign skin lesions and served, therefore, as a control group. The peripheral blood smears were considered to be positive when > 20% of the circulating lymphocytes were atypical convoluted lymphocytes.

RESULTS

The results of cytogenetic studies on peripheral blood cells are shown in table 1. Two patients with cutaneous plaques or tumors and all 14 patients with erythroderma had positive peripheral blood smears. Aneuploidy was definitely present in 11 of these 16 patients. One additional patient had at least two abnormal metaphases. No mitoses were present in one patient and three patients had only normal diploid metaphases. Twenty patients with plaques and tumors had negative peripheral blood smears. Aneuploidy was observed in ten of these patients, four had no mitoses, and six had only normal metaphases. Thus, aneuploidy was observed in 12 (75%) of 16 patients with positive peripheral blood smears and in ten (50%) of 20 with negative peripheral blood smears.

The cytogenetic results from lymph node cells are shown in table 2. Aneuploidy was present in 17 of 20 samples including all patients with erythroderma and eight of 11 with cutaneous plaques and tumors.

Cytogenetic results from the bone marrow samples are shown in table 3. Aneuploidy was present in only five of 31 samples. Only one of these five patients had morphologic evidence of bone marrow involvement. Thus, although aneuploidy was infrequent in bone marrow samples, it was present in some morphologically normal marrows.

Detailed banding analysis was possible in five patients with generalized plaques and nine patients with erythroderma as shown in tables 4 and 5.

Of the patients with generalized plaques, two were hypodiploid and the other three showed either hypodiploidy and hyperdiploidy, pseudodiploidy, or pseudodiploidy and hyperdiploidy. Structural aberrations were seen in chromosomes 1, 3, 4, 5, 6, 9, 10, 11, and 17, plus minutes; chromosomes 10, 9, 15, 21, 8, 11, 12, 13, 16, 17, 18, 20, and 22 were involved in numerical abnormalities (listed in order of frequency).

TABLE 2.—Cytogenetic results in lymph node

Morphologically positive	No. of samples	Cytogenetic results*			
		+	±	–	NM
Plaques or tumors	11	8	0	2	1
Erythroderma	9	9	0	0	0

*See table 1 for definitions.

TABLE 3.—Cytogenetic results in bone marrow

	No. of samples	Cytogenetic results*			
		+	±	–	NM
Morphologically positive					
Erythroderma	1	1	0	0	0
Morphologically negative					
Plaques or tumors	20	0	2	18	0
Erythroderma	10	2	0	8	0

*See table 1 for definitions.

TABLE 4.—Chromosome abnormalities in generalized plaques (5 patients)*

	No. of patients	Samples from—
Hypodiploid	2	Lymph node, peripheral blood
Hypodiploid and hyperdiploid	1	Lymph node
Pseudodiploid	1	Peripheral blood
Pseudodiploid and hyperdiploid	1	Bone marrow, peripheral blood

*Structural aberrations in chromosomes 1, 3, 4, 5, 6, 9, 10, 11, 17, minutes; numerical abnormalities in chromosomes 10, 9, 15, 21, 8, 11, 12, 13, 16, 17, 18, 20, 22.

Ploidy in the nine patients with erythroderma or the Sézary syndrome is shown in table 5. Four patients had hypodiploidy, two had hypodiploidy and hyperdiploidy combined, and the following deviations from diploidy were seen in one patient each: hypodiploidy and pseudodiploidy, pseudodiploidy and hyperdiploidy, and near-tetraploidy. This table reveals that the chromosomal abnormalities seen in the patients with the Sézary syndrome were more extensive than those seen in the group with generalized plaques. Every chromosome, not excluding the sex chromosomes, were involved in structural and/or numerical rearrangements (ring and minute chromosomes were also seen), the most frequently involved being chromosomes 1 and 7. Abnormalities of chromosome 1 from seven patients are shown in figure 1. Four of the patients (Nos. 1, 3, 4, and 5) had received systemic chemotherapy prior to cytogenetic analysis; the remaining patients were untreated. All patients with the exception of No. 7 had the Sézary syndrome. The marker chromosome involved either chromosome 1 alone or its rearrangement with other chromosomes such as 2, 7, or 17. Only two patients had similar abnormalities: patients 2 and 3 both had a lp+ marker but patient 3 had a lp+q– marker in addition. In patients 3 and 4, the markers seen in the lymph nodes were identical to those seen in the peripheral blood.

TABLE 5.—Chromosome abnormalities in erythroderma (Sézary syndrome) (9 patients)

	No. of patients	Sample from—
Hypodiploid	4	Lymph node (2), peripheral blood (2)
Hypodiploid and pseudodiploid	1	Lymph node
Hypodiploid and hyperdiploid	2	Lymph node
Pseudodiploid and hyperdiploid	1	Lymph node
Near-tetraploid	1	Peripheral blood

*Structural aberrations in chromosomes 5x (1, 7), 4x (14, 16), 3x (6, 9), 2x (4, 15), 1x (X, 2, 3, 12, 13, 17, 18, 19, 20, 21, ring); numerical abnormalities in chromosomes 5x (8), 4x (11, 15), 3x (10, 17, 21), 2x (2, 6, 9, 12, 13, 18, 20), 1x (3, 5, 14, 16, 22, Y, minute).

The cytogenetic results in the four patients who served as controls are listed in table 6. Abnormalities were found in only one instance: patient 10 with alopecia mucinosa had 10% aneuploidy in his peripheral blood. The other three patients had either normal karyotypes or no mitotic figures in their cytogenetic preparations.

DISCUSSION

Cytogenetic studies in CTCL patients showed aneuploidy in 17 (85%) of the 20 lymph nodes, 23 of the 36 peripheral bloods, and five of the 31 bone marrows. Cytogenetic studies were abnormal in nearly all positive peripheral blood samples as well as in five patients with negative smears. Aneuploidy was observed in four of the 30 negative bone marrow samples. These findings indicate that cytogenetic studies can be very useful in the early detection of malignant cells, even when only a low percentage of such cells can be detected in the peripheral circulation. The lymph node findings demonstrate that malignant cells are found in nearly all enlarged lymph nodes. Seven of the eight

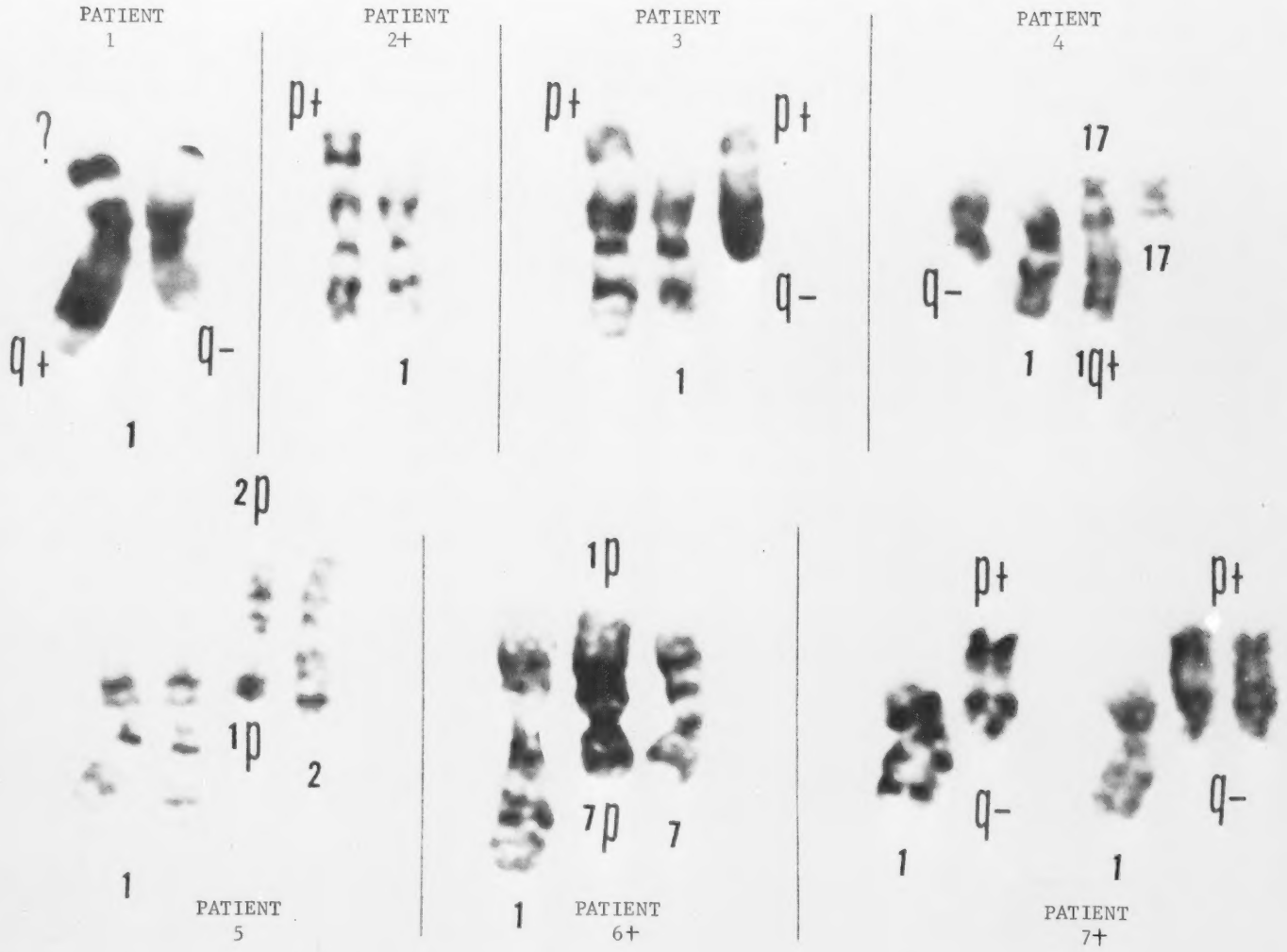

FIGURE 1.—Chromosome 1 abnormalities in 7 patients. "+" indicates patients who had received no prior systemic therapy.

TABLE 6.—Cytogenetic studies in 4 control patients

Patient No.	Diagnosis	Samples from—*		
		Bone marrow	Peripheral blood	Lymph node
8	Parapsoriasis	N	N	—
9	Lymphomatoid granulomatosis	N	NM	NM
10	Alopecia mucinosa	—	Aneuploidy (10%)	—
11	Lymphomatoid papulosis	N	N	N

*N = normal; NM = no mitoses.

nodes with detailed banding results had hypodiploid cells.

Seven patients had marker chromosomes which were at least partially derived from chromosome 1; three of these patients had received systemic chemotherapy and the remaining patients were untreated. It can be stated, therefore, that aneuploidy is present in the early course of the disease, prior to treatment. Chromosome 1 abnormalities have been reported in various hematologic disorders (10–15) as well as in cases of ovarian cancer (16) and in malignant effusions (17). The wide-spread occurrence of abnormalities of this chromosome in malignant disease suggests an association between this chromosome and malignant transformation, regardless of histopathologic type.

Cytogenetic studies in these patients demonstrate that, in most instances, aneuploidy was extensive, with both numerical and structural abnormalities, a wide range of heteroploidy, and a lack of clone formation until the terminal phase of the disease. The structural aberrations involved chromosome 1 most often, followed by 7, 14, 16, 6, and 9 (in order of frequency). Chromosomes 8, 15, 11, 17, 21, and 10 were those most frequently involved in numerical aberrations.

Patient 10 with alopecia mucinosa had 10% aneuploidy in his peripheral blood. At the present time, his skin biopsies are suspicious for CTCL but are not diagnostic. Cytogenetic studies may be able to assist in identifying these early cases.

A high incidence of aneuploidy was noted in these CTCL patients, not only in skin lesions but also in peripheral blood, lymph node, and occasionally bone marrow. The aneuploidies in patients with plaques and tumors (mycosis fungoides) and generalized erythroderma (Sézary syndrome) were similar in type, but in the Sézary syndrome the abnormalities were more common and extensive and more frequently exhibited clonization. This leads us to believe that the two diseases are actually different clinical manifestations of the same disease, the Sézary syndrome being the more advanced of the two.

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Experience With Lymphography in Patients With Mycosis Fungoides [1]

Ronald A. Castellino,* Richard T. Hoppe, Norman Blank, Stuart W. Young, and Zvi Fuks [2]

Our experience with lymphography in patients with mycosis fungoides (MF) is analyzed in this report. For detailed information regarding the pathology, staging, and treatment of MF, reference should be made to the appropriate papers published in this issue.

The clinical variables and therapeutic regimens pertaining to patients with MF seen at the Stanford University School of Medicine can be found in the paper by Hoppe et al (1). The patients analyzed in this study were drawn from this group as well as from groups of patients previously reported by Fuks et al (2,3). Only about one half of the patients with MF seen at the Stanford Medical School are referred for bipedal lymphography. Many patients did not have lymphangiograms (LAGs) either because (*a*) the procedure was not considered to be of potential clinical value, or (*b*) the patients had medical contraindications, especially severe underlying pulmonary disease, or extensive skin involvement in the region of the planned lymphatic cannulation. Of all patients undergoing lymphography, the radiographs could be retrieved for review in 97 cases and it is this material which is the subject of this paper.

MATERIALS AND METHODS

The extent of skin involvement for the 97 patients in this study is shown in table 1. Since only five cases were of the lichenoid type, they have been excluded from subsequent analysis. As anticipated, the incidence of palpable lymph nodes increases with increasing severity of the disease (table 1).

The films from the LAG of these 97 patients were reviewed without prior knowledge of clinical data except for a confirmed histologic diagnosis of MF. Analysis of the appearance of the opacified lymph nodes was based upon anatomic location as well as internal architectural characteristics. The lymph nodes were arbitrarily divided into four anatomic groups (fig 1):

1) *Femoral* (lying caudad to the inguinal ligaments).
2) *External iliac* (lying between the approximate point of bifurcation of the common iliac artery at the inferior aspect of the sacrum to the inguinal ligament).
3) *Common iliac* (lying between the level of the aortic bifurcation and the common iliac bifurcation).
4) *Para-aortic* (cephalad to the aortic bifurcation).

The internal architecture was evaluated and assigned to one of four categories (fig 2):

0 = "*Normal*" (homogeneous, fine, stippled pattern).
I = *Minimal hyperplasia* (slight nodal enlargement with a prominent granular pattern not infrequently seen in patients undergoing lymphography for a wide variety of other reasons).
II = *Marked hyperplasia* (moderate lymph node enlargement with striking granularity evenly distributed throughout the opacified nodes in each group).
III = "*Lymphoma*" *pattern* (enlarged lymph nodes with frank foaminess or focal areas of replacement).

Following categorization of the LAG, correlations were made with (*a*) extent of skin involvement, (*b*) patterns of involvement at each lymph node anatomic site for the extent of skin involvement, (*c*) presence or absence of palpable lymphadenopathy

TABLE 1.—Extent of skin involvement and incidence of palpable lymph nodes

Extent of skin involvement	No. of— Patients in the study	Patients with palpable lymph nodes
Limited plaque	20	4 (20%)
Generalized plaque	38	20 (53%)
Lichenoid	5	3
Erythematous	15	14 (93%)
Tumorous	19	16 (84%)
	97	57 (59%)

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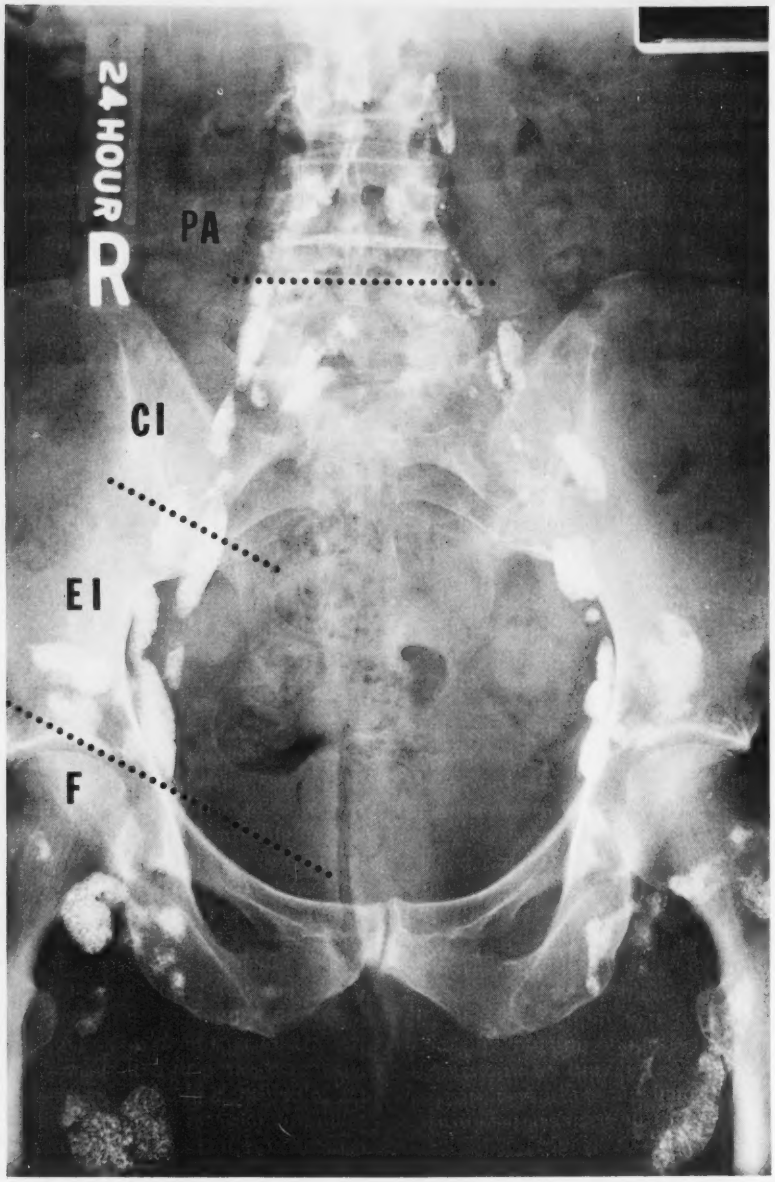

FIGURE 1.—Frontal view of an LAG of a 53-yr-old woman with MF. The anatomic lymph node sites used in this study are indicated by F (femoral), EI (external iliac), CI (common iliac), and PA (para-aortic). Note the increasing severity of lymph node abnormalities progressing distally.

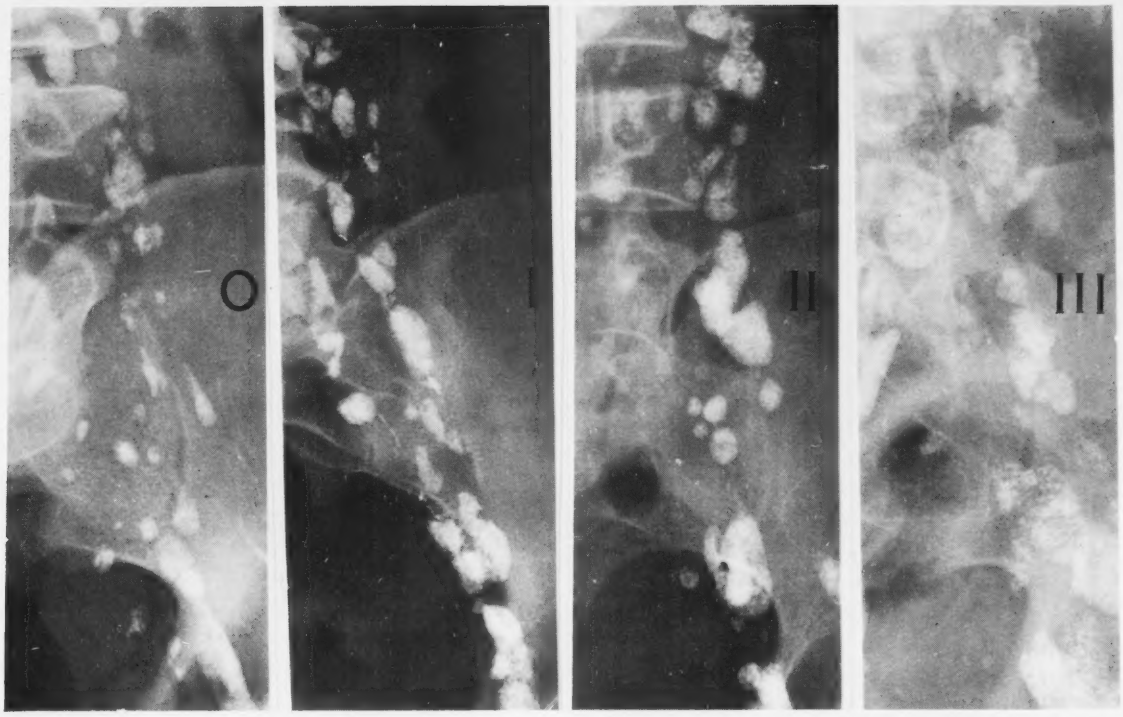

FIGURE 2.—Left posterior oblique views of LAGs in 4 patients showing the progressive abnormalities of lymph node internal architecture and size as graded in this study (grades 0, I, II, and III; *see* text for details).

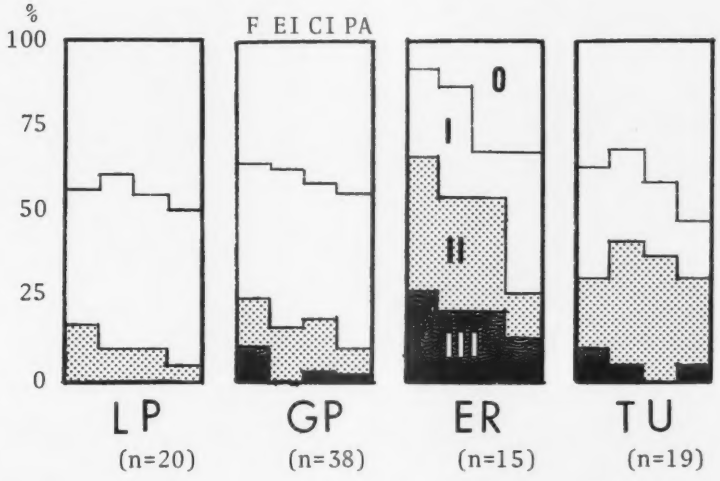

FIGURE 3.—Incidence of lymphographic abnormalities (grades 0, I, II, and III) encountered at each anatomic site (F = femoral, CI = common iliac, EI = external iliac, PA = para-aortic) for each clinical extent of skin disease (LP = limited plaque, GP = generalized plaque, ER = erythematous, TU = tumorous). Note the increasing severity of lymphographic grade with increasing extent of skin disease, as well as the increasing lymph node abnormalities in the more distal lymph node groups.

TABLE 2.—Frequency of lymphographic patterns

LAG grade	Extent of skin involvement: Limited plaque	Generalized plaque	Erythematous	Tumorous	Totals
0	9	13	4	7	33
I	9	17	3	4	33
II	2	7	5	7	21
III	—	1	3	1	5
Totals	20	38	15	19	

at the time of presentation, (*d*) results of biopsies of lymph nodes opacified at lymphography, and (*e*) freedom from relapse.

RESULTS

The frequency of the lymphographic patterns (grades 0, I, II, and III) in the four clinical groups is shown in table 2, and the incidence of the patterns per anatomic site is shown in figure 3. The highest incidence of grade III LAGs occurred in the erythematous group whereas none was encountered in the patients with limited plaque disease. In general, the lymph nodes showed the greatest degree of abnormality in the femoral region with less extensive abnormalities in the more proximal nodal groups (fig 1).

Palpable lymphadenopathy was present in 54 of 92 patients (59%). The likelihood of palpable lymphadenopathy increased directly as the lymphographic grade increased ($P = 0.0004$; Fisher exact test) (table 3). Fifty percent of the patients with grade 0 and I LAGs had no palpable lymphadenopathy, whereas 81% (21 of 26) of those with grade II and III LAGs had palpable lymph nodes. Similarly, 39% (21 of 54) of the patients presenting with palpable lymph nodes had grade II and III LAGs, whereas 87% (33 of 38) of those without palpable adenopathy had grade 0 and I LAGs.

TABLE 4.—Correlation of LAG grade with results of biopsy of opacified lymph nodes in 24 patients

Biopsy results	No. of patients with LAG grade—: 0	I	II	III
Normal	3	2	2	
Dermatopathic lymphadenitis	1	5	4	3
MF			2	2

Twenty-four patients had biopsies of opacified lymph nodes within several weeks of the LAG (table 4). The sample size is small, but the four patients with lymph node involvement by MF had grade II or III LAG, whereas five of the seven patients with normal biopsies had either grade 0 or I LAG. Dermatopathic lymphadenitis was seen in all LAG grades, but in only one of 13 cases was the LAG grade 0.

The 38 patients with generalized plaque disease were analyzed to assess the correlation of the lymphographic appearance with the probability of freedom from relapse (fig 4). Although patients with grade 0 and I LAGs appear to have a greater probability of freedom from relapse, the difference was not statistically significant ($P = 0.39$; Gehan test).

DISCUSSION

Lymphography is an extremely useful staging technique in patients with Hodgkin's disease and non-Hodgkin's lymphoma. For this reason, this procedure has been used by some groups in patients with MF. We are aware of three published papers describing such experience (28 patients from Stanford University Medical Center in 1974 [3], 44 patients from Temple University in 1974 [4], and ten patients from Helsinki University Hospital in 1977 [5]). The reported experience, including the present study which encompasses 97 patients, is still relatively small, particularly when the various clinical stages are analyzed.

TABLE 3.—Correlation of LAG with palpable lymph nodes*

LAG grade	Extent of skin involvement: Limited plaque	Generalized plaque	Erythematous	Tumorous	Totals
0	2/9	6/13	3/4	4/7	15/33 (45%)
I	2/9	9/17	3/3	4/4	18/33 (54%)
II	0/2	5/7	5/5	7/7	17/21 (81%)
III	—	0/1	3/3	1/1	4/5 (80%)
	4/20	20/38	14/15	16/19	54/92 (59%)

*No. of patients with palpable lymph nodes/No. of patients in clinical and LAG stage.

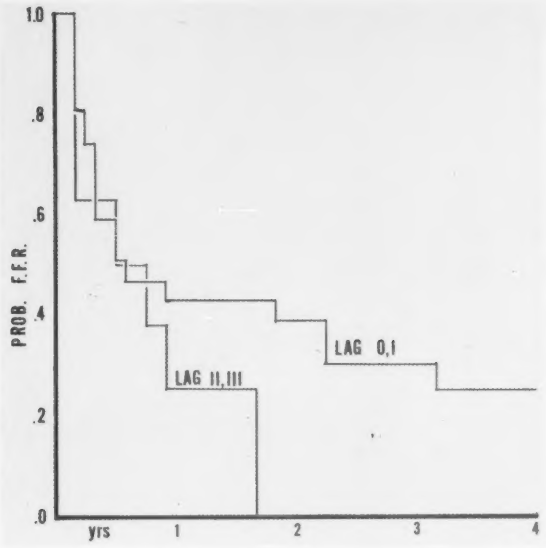

FIGURE 4.—Probability of freedom from relapse for the 38 patients with generalized plaque disease according to their LAG grade. Although patients with LAG grades 0 and I appear to do better than those with grades II and III, this difference is not statistically significant.

From our data, it appears that our experience with lymphography has contributed little to the clinical management of patients with MF or to the basic understanding of this disease. Lymphography might be expected to provide valuable information since clinical experience has shown that patients with MF who have palpable lymphadenopathy have a poorer prognosis, whether or not the enlarged lymph nodes contain light microscopic evidence of MF or simply dermatopathic lymphadenitis. Our study has shown that the abnormalities on the LAG do parallel the advancing clinical extent of disease, so that patients with limited or generalized plaque disease have more normal-appearing studies than those with either erythematous or tumorous disease.

The increasing incidence of lymphographic abnormalities also parallels the presence of palpable lymph nodes. Half of our patients with grade 0 or I LAG had no palpable lymph nodes and 81% with grade II or III LAG had palpable lymphadenopathy. Perhaps the 13% of patients (five of 38) without palpable nodes who had grade II and III LAGs represent a clinical underestimation of disease, since the intra-abdominal and pelvic lymph nodes are not accessible to palpation. In the one subgroup

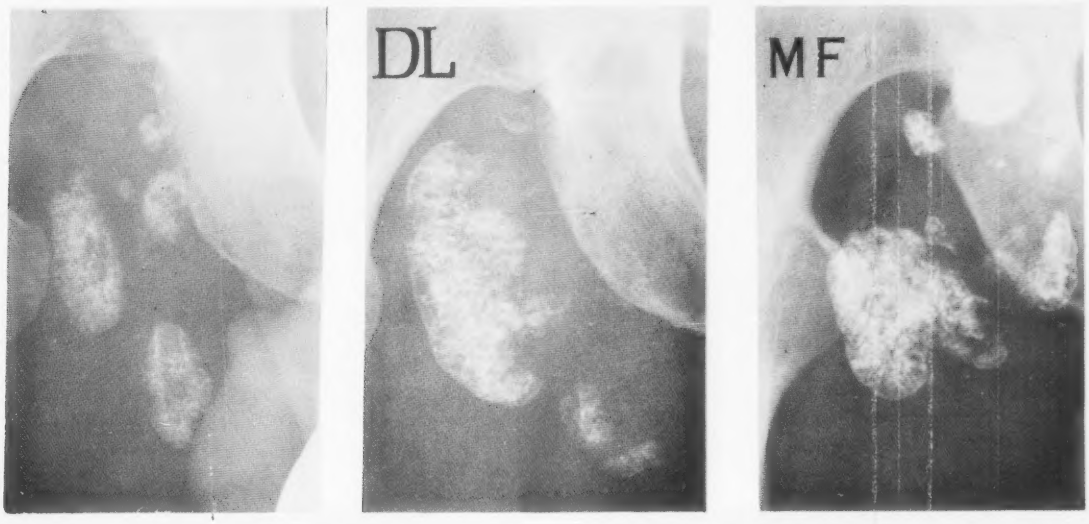

FIGURE 5.—Frontal views of the opacified femoral lymph nodes of 3 patients with MF. There is marked distortion of the internal architecture of the lymph nodes shown by biopsy to be involved with dermatopathic lymphadenitis (DL) and MF compared to the more normal reactive appearance of the typical femoral nodes (left). Also note that the lymph nodes involved with DL are architecturally more disturbed than those involved with MF.

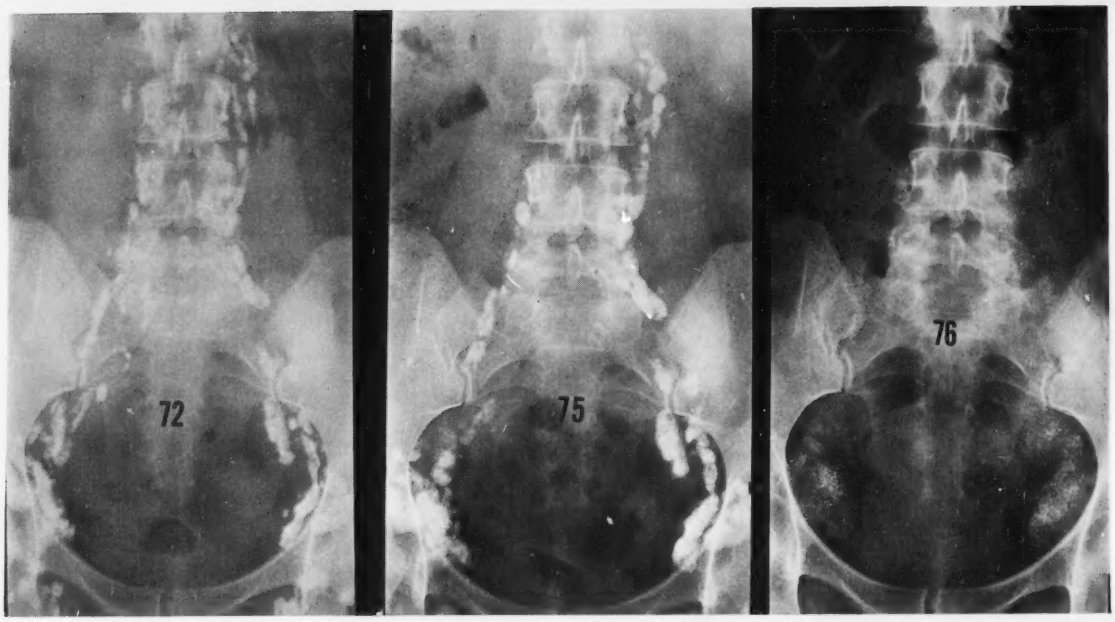

FIGURE 6.—A 72-yr-old woman with generalized plaque disease had a normal LAG in 1972. A repeat study in 1975 showed interval increase in lymph node size with internal architectural changes at many sites, particularly in the left para-aortic and low pelvic regions, interpreted as being positive. A surveillance abdominal film in 1976 showed progressive increase in size of the residually opacified lymph nodes interpreted as progression of disease from which the patient died (at autopsy the lymph nodes were diffusely involved with MF).

in which an analysis of probability for freedom from relapse was possible, the lymphographic grade had no prognostic significance statistically.

The patients who had lymph node biopsy where a direct lymphographic-pathologic correlation could be made demonstrated no clearcut correlation between the lymphographic appearance and the lymph node histology, based upon the lymphographic grading criteria used in this study (fig 5). However, the more abnormal-appearing lymph nodes on lymphography do have a greater incidence of involvement with MF or dermatopathic changes when compared to the more lymphographically normal-appearing nodes which are usually normal histologically.

In conclusion, we believe our data suggest that in MF lymphography contributes little to staging of disease, to modification of treatment planning, or to elaboration of prognosis. Variables which are at present readily evaluated clinically serve these functions so that little additional information is gained from the results of lymphography. Because lymph nodes remain opacified for many months after the LAG, however, this technique could provide useful information in a selected group of patients for whom disease relapse or response to treatment could be objectively monitored (fig 6). This might become more important should systemic therapy or deep radiotherapy become more routinely utilized treatment modalities. Lymphography might still be utilized in evaluating patients with MF in centers in which ongoing clinical research protocols are being conducted to further evaluate the potential value of this technique in this disease.

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In Vitro Growth of Cutaneous T-Cell Lymphomas

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SUMMARY

It is relatively easy to propagate EB virus-transformed normal and malignant B lymphocytes in vitro. Normal T lymphocytes divide for short periods of time after exposure to many mitogens. Exposure of normal T lymphocytes to lymphocyte-conditioned medium (LCM) permits them to divide for longer periods of time, but permanent cell lines cannot be established. Initial attempts to grow malignant T cells from patients with cutaneous T-cell lymphomas (CTCL) in unsupplemented growth medium resulted in the establishment of four EB virus-transformed B-lymphoblastoid lines. The responses of CTCL cells to mitogens and LCM varied from unresponsive to near normal. Subsequent attempts to grow CTCL cells in medium supplemented with mitogens or LCM resulted in the establishment of two cell lines lacking B-cell markers or EB virus. The cells of both lines initially had the ability to form E rosettes, although one of the lines has lost this ability with passage. The two lines can be distinguished from normal T cells by having some or all of the following properties: long-term proliferation, tumorigenicity in nude mice, gradual loss of dependence on mitogen or LCM, and convoluted nuclear morphology.

[Cancer Treat Rep 63:587–590, 1979]

Although > 200 lymphocyte lines have been established in long-term culture, most of these have been B lymphoblastoid (1). Lymphoblastoid cells are diploid polyclonal B lymphocytes transformed in vitro by EB virus present in the blood or tissues of seropositive patients (2). Malignant lymphoid cells, other than from Burkitt's lymphoma, are difficult to establish in long-term culture (2). Initial growth is frequently aided by factors released by other cells (3,4). Normal thymus-dependent (T) lymphocytes lack receptors for EB virus, and cannot be transformed by it. T cells undergo blast cell transformation when exposed to a variety of mitogens (5). Some of the transformed cells divide, but prolonged exposure is toxic. Relatively few lines have been established from T-cell malignancies, and most have been from young patients with acute lymphoblastic leukemia (6,7).

The cutaneous T-cell lymphomas (CTCL) consist of mycosis fungoides (MF), Sézary's syndrome, and related disorders (8). The neoplastic cells have membrane features of T lymphocytes, a tendency to infiltrate the skin, and characteristic nuclear morphology (8). CTCL cells have not been established in long-term cultures, and experimental models do not exist. Biologic studies of this fascinating group of disorders have been limited to clinical observations and short-term in vitro studies using circulating Sézary cells. In this paper, we describe the requirements of mitogens or lymphocyte-conditioned medium (LCM), a blastogenic factor released by stimulated T cells (9), for the successful long-term propagation of CTCL cells.

MATERIALS AND METHODS

Tumor Source

Neoplastic CTCL cells were obtained from biopsies of involved lymph nodes of patients with MF and

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[2]We thank Cynthia Ziskie for helping to establish one of the cell lines, and Harvie Sims and Frances Soehnlen for technical assistance.

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circulating cells were obtained from patients with Sézary's syndrome. Lymph node cells were disaggregated by passing them through a cytosieve (pore size, 70 μ). Mononuclear peripheral blood cells were obtained by Ficoll-Hypaque density-gradient centrifugation of heparinized blood. The percentage of convoluted cells with atypical nuclei was determined by examining air-dried, Wright-Giemsa-stained smears. Specimens containing $< 1 \times 10^7$ atypical lymphocytes were considered unsatisfactory, and their data were disregarded.

Culture Methods

Mononuclear cells were seeded into plastic flasks at a density of 1×10^6/ml in RPMI-1640 medium (GIBCO, Grand Island, NY) containing 20% heat-inactivated fetal bovine serum (growth medium). Replicate flasks were supplemented with mitogens or LCM. The medium was changed every 7 days. Cells were harvested and passaged whenever an approximately tenfold increase in cell density occurred. If considerable debris and dead cells were present, they were removed by Ficoll-Hypaque centrifugation followed by three rinses in phosphate-buffered saline prior to passage. Once established, cell lines were maintained in medium supplemented with 5% or 10% serum. Cells were maintained in a water-jacketed humidified incubator at 37°C, in an atmosphere of 5% CO_2 and 95% air.

Mitogens and Lymphocyte-Conditioned Medium

Phytohemagglutinin (PHA-M) was purchased from GIBCO, and concanavalin A (CON A) was purchased from Pharmacia (Piscataway, NJ). LCM was prepared by a modification of the method of Morgan et al (9). Mononuclear cells were obtained from the blood of normal donors, pooled, and cultured (1×10^6/ml) in RPMI-1640 medium supplemented with 1% PHA-M and 1% autologous serum. Fluids were collected 3 and 6 days later, clarified by centrifugation, dialyzed against phosphate-buffered saline, concentrated fivefold, millipore filtered, aliquoted, and stored at −20°C until used.

Lymphocyte Characterization

E-rosette formation was performed according to the method of Kaplan and Clark (10), using AET-treated sheep rbcs. Surface immunoglobulin (SIg) was detected by a direct fluorescent method, using fluorescein-labeled goat polyvalent antihuman immunoglobulin (Meloy Laboratories, Springfield, Va). Complement (C′) receptors were tested for by the technique of Gelfand et al (11), using fluoresceinated *Salmonella* coated with complement. The presence of EB virus-associated nuclear antigen (EBNA) was tested for by the method of Reedman and Klein (12). EBNA tests were kindly performed by Dr. Paul Feorino, National Center for Disease Control, Atlanta, Ga.

Tumorigenicity

The tumorigenicity of fresh and cultured cells was determined by injecting 1×10^7 cells ic into 4–6-week-old athymic nude mice obtained from A. R. Schmidt Co, Madison, Wis.

Determination of Ploidy

Actively growing cells were treated with colchicine (0.1 μg/ml) for 2 hours, exposed to hypotonic potassium chloride (0.075 M) for 10 minutes, fixed in ethanol-acetic acid (3:1), and stained with Wright-Giemsa. The chromosome numbers of 20–25 well-spread metaphases were determined for each line.

RESULTS

Tumorigenicity of Cutaneous T-Cell Lymphoma Cells

Cell suspensions of tumor-involved lymph nodes from seven MF patients were injected ic into a total of > 100 nude mice. One mouse developed progressive disability of gait after 3 months and was killed. A few small meningeal plaques consisting of lymphoid cells were noted on histologic examination. The other mice remained healthy during observation periods ranging from 3 to 6 months. Additional nude mice injected intradermally, ip, and sc failed to develop evidence of disease.

Establishment of B-Lymphoblastoid Cell Lines

In initial experiments, 13 CTCL specimens were cultured in growth medium without additives. Cultures from four patients exhibited progressive, vigorous growth after latent periods of 4–6 weeks. All four patients had properties of lymphoblastoid cell lines (1), having SIg, C′ receptors, and EB virus (table 1). The lines did not form E rosettes. All four lines were diploid initially, but one became aneuploid after long-term passage. All three of the lines tested for tumorigenicity formed invasive and meningeal tumors, and killed the nude mouse recipients 5–8 weeks later. Wright-Giemsa-stained air-dried smears revealed large cells with high nuclear-cytoplasmic ratios, dark blue cytoplasm, and round nuclei containing one to four prominent nucleoli.

TABLE 1.—Comparison of T- and B-cell lines established from CTCL patients

	EB virus	SIg	C′ receptors	E rosettes	Ploidy	Tumorigenicity (nude mice)	Nuclear morphology
B-cell lines	+	+	+	–	Diploid → aneuploid	+	Round
T-cell lines	–	–	–	+	Diploid or aneuploid	+	Round or convoluted

Growth of T-Cell Lines

After culture of the first 13 specimens failed to grow T cells, replicate flasks of the next six tumor specimens were also cultured in the presence of PHA-M (1%–10%), CON A (1–10 μg/ml), and LCM (5%–20%). Three of the six exhibited growth in some of the flasks with additives, and the cultures with the most growth were passaged. Cell lines from two of these cultures have been maintained for 6–8 months. Growth of these lines has been variable, with periods of vigorous growth followed by periods of slow replication and cell death (crises). The cells surviving the crises have become progressively less dependent on the presence of additives. Currently, replicate cultures are maintained with and without additives. One line was initiated with the addition of CON-A, and the other line was initiated with the addition of LCM. The lines lack B-cell markers (table 1). Both lines formed E rosettes initially, but one has lost this ability with passage. One of the lines has a large tetraploid population and a smaller diploid population; the other has a diploid number of chromosomes. The line with the aneuploid subpopulation formed intracranial tumors in nude mice after latent periods of 10–12 weeks. Tumor explants from the nude mice were successfully re-cultured and revealed only tetraploid cells. Mice injected with the other line remain healthy 12 weeks later. Air-dried smears of the line with the aneuploid subpopulation reveal many cells (20%–30%) with convoluted nuclei; the diploid line has fewer cells with convoluted nuclei (5%–10%). The remaining cells have round nuclei with one to three nucleoli.

DISCUSSION

The failure of heterotransplanted CTCL cells to grow in athymic nude mice and the lack of a suitable animal model for the disease suggests that experimental studies may be limited to in vitro systems. Our data confirm that B-lymphoblastoid lines, from normal or tumor sources, are relatively easy to establish in long-term culture. Except for Burkitt's lymphoma, these lines represent in vitro transformation of nonmalignant B cells by EB virus (1,2). The lines have B-cell markers and the EB genome. They are diploid, but with continued passage may become aneuploid (13). It is of interest to note that Levy et al (14) also established a B-lymphoblastoid culture from a lymph node of a patient who subsequently developed MF.

Routine tissue culture methodology is usually insufficient for the growth of T cells, and only a handful of lines have been established from T-cell malignancies, mainly acute lymphoblastic leukemia. LCM is required for the growth of normal T cells, but the cells remain completely dependent on the continued presence of LCM, and continuous lines have not been established from normal T cells. Short-term exposure to many mitogens induces blast cell transformation and mitosis in a high percentage of T cells, but long-term exposure is toxic. Mitogens are also required for T-cell colony formation in semi-solid media (15). Our studies demonstrate that exposure to mitogens or LCM induces division in the cells of some cases of CTCL. With the use of these factors, we have established two T-cell lines in long-term culture and have induced at least temporary growth in one other. The latter has been subpassaged, but cannot be considered as an established line. The heterogeneous responses of CTCL cells to mitogens as well as their variable responses to individual mitogens (Carney et al, in preparation) are reflected in our findings that factors induced growth in three of six cases, but that the factor inducing optimal growth varied in each case (CON A, PHA-M, and LCM). Factor-dependent growth of CTCL requires either a "shotgun" approach, using multiple mitogens at several concentrations, or a more selective approach, determined by pretesting the cells by the lymphocyte transformation assay. In contrast to the B-lymphoblastoid lines, in which continuous vigorous growth occurred after a latent

TABLE 2.—Properties of T-cell lines

	Normal T cells	CTCL lines
Growth	Limited	> 6 mos
Dependence on mitogen or LCM	Absolute	Only initially
Ploidy	Diploid	Diploid or aneuploid
Tumorigenicity (nude mice)	?	Intracranial
Nuclear morphology	Round	Round or convoluted

period, factor-induced T-cell growth was immediate but intermittent, with growth cycles alternating with crises.

One of the cell lines is tumorigenic and has tetraploid and diploid subpopulations; the other line is diploid. Detailed cytogenetic analyses will be required to determine whether these populations are diploid or pseudodiploid. Table 2 shows the differences between the lines and LCM-stimulated normal T cells. The latter remain absolutely dependent on LCM and proliferate for a finite time. Mitogen-induced T-cell proliferation can only be maintained for one or two passages. LCM-stimulated normal T cells are diploid and nontumorigenic. In contrast, one of our lines is tumorigenic and has a tetraploid subpopulation. The lines have gradually become factor-independent. Initiation of CTCL proliferation requires T-cell mitogens or LCM. The initial growth of histiocytic lymphomas is frequently aided by a variety of factors, but with passage the cells become independent of them (3,4). We have not systematically tested nonspecific factors such as feeder layers, human sera, effusion fluids, etc. The CTCL lines have a percentage of cells with convoluted nuclei, in contrast to LCM-stimulated normal T cells. It is not known whether these cells reflect the convoluted cells characteristic of the CTCL syndromes, or whether they are present in many, or all, malignant T-cell lines (16).

The establishment and characterization of CTCL lines may provide important new insights into the biology of normal and malignant T cells.

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Exposure to Chemicals, Physical Agents, and Biologic Agents in Mycosis Fungoides and the Sézary Syndrome

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SUMMARY

The history of occupational, environmental, and/or iatrogenic exposure to potential carcinogenic agents was obtained at the time of onset of skin disease in 43 of 44 patients with cutaneous T-cell lymphoma (mycosis fungoides and the Sézary syndrome) entering a National Cancer Institute therapeutic trial. A history of multiple exposures to these agents was common, the two most frequent being chemicals (91% of patients) and drugs (86%). Mean duration of exposure was 13 years for chemicals and 18 years for drugs. The most common chemicals were air pollutants (39%), pesticides (36%), solvents and vapors (30%), and detergents and disinfectants (14%). Increased severity of disease was seen with increased duration of chemical exposure in stage V cutaneous T-cell lymphomas only. The most frequent drugs besides tobacco (86%) were analgesics (20%), tranquilizers (18%), and thiazides (14%). Second cancers occurred in four patients, including two renal cell carcinomas, and a family history of cancer was present in 11. Fourteen of 22 patients questioned had recurrent herpes simplex. Patients with chronic skin disease who have long-term exposure to combinations of chemicals, physical agents, and biologic agents, are heavy smokers, or have recurrent herpes simplex appear to be prime candidates for developing mycosis fungoides or the Sézary syndrome.

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Mycosis fungoides, the Sézary syndrome, and lymphomatoid papulosis are all cutaneous T-cell lymphomas (CTCL). There have been important advances in understanding the biology (1–3) and treatment (4–7) of CTCL, but the etiology remains speculative (8–10). In other cancers several environmental factors appear to have an etiologic role (11), including tobacco (12), asbestos (13), and air pollution (14) in lung cancer, alcohol in laryngeal cancer (15), and radiation in leukemia in radiologists (16). In addition, host factors contributing to etiology include familial susceptibility (17) and multiple primary neoplasms (18).

The aim of the present study was to search for possible environmental, iatrogenic, and host factors in the causation of this group of diseases. The study was prompted by the observation, in four of our patients who are described in this report, that the onset of CTCL was preceded by clear-cut environmental or iatrogenic chemical exposure.

METHODS

Patient Selection

Forty-four patients with histologically confirmed mycosis fungoides or Sézary syndrome were seen at the National Cancer Institute-Veterans' Administration Medical Oncology Branch for entry into an approved human experimentation protocol between July 1976 and November 1978. Patient characteristics included the following: 26 males and 18 females;

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32 whites and 12 blacks; and a mean age of 52 years (range, 22–75 years). The study included veteran and non-veteran patients. Patients underwent routine pretreatment staging procedures including (*a*) complete history and physical examination; (*b*) cbc, platelet, differential, and absolute lymphocyte counts, and review of lymphocytes for "convoluted nuclei"; (*c*) serum chemistries, liver and renal function tests, and uric acid levels; (*d*) chest roentgenogram and lymphangiogram; (*e*) radionuclide liver and spleen scans; and (*f*) biopsies of skin, lymph nodes (if palpable), bone marrow, and liver (if needle biopsy was negative, peritoneoscopy with multiple liver biopsies was performed).

Staging

Stages of disease, as outlined by Van Scott et al (19), were defined as I (limited plaques on < 10% of the body surface, no lymphadenopathy, and no systemic involvement); II (generalized plaques on > 10% of the body surface without extracutaneous involvement); III (tumors or ulcers on skin, no lymphadenopathy, and no systemic disease); IV (lymphadenopathy); and V (visceral disease).

Histories

After patient selection, detailed histories based on the National Cancer Institute Epidemiology Branch questionnaire (20) were obtained by one of the investigators (Dr. Fischmann). Patient histories revealed exposure to chemicals, iatrogenic drugs, radiation, and allergens. A chemical was defined as a natural or synthetic substance obtained or used in chemical operations (21). Classification of chemicals followed that of Casarett and Doull (22). Duration of exposure to agents was assessed as in case 3 (*see* below) and was quantified in hours. Air pollution was considered contamination of the atmosphere by noxious chemicals or particulate matter (eg, dust from coal or fabrics).

RESULTS

The four cases which stimulated our interest in agent exposure are presented below.

Case 1.—A 36-year-old white male had had a skin eruption since 1961. In 1960, he began work with a pile-driving firm in Florida. Three or four times a year he worked with creosote-impregnated piles and the patient noted that all the workers received creosote burns. After 1 year he had a rash on his left hip, immediately beneath the pocket in which he kept creosote-soaked objects. The rash spread to his arms, legs, and trunk. The initial hip lesion always remained his worst lesion. Finally, on entering the work yard in hot weather his skin would burn if creosote logs were stacked in the yard. A diagnosis of poikilodermatous mycosis fungoides was made in 1972. We estimated that he had an equivalent of approximately 140 hours of continuous exposure to creosote over 5 years.

Case 2.—A 73-year-old white female had had an erythroderma for 5 years. As a child she helped her siblings spray potato plants with Paris green (an arsenic insecticide). Their clothes always got saturated with the solution. We estimated that she had the equivalent of 26 hours of exposure over 5 years. For 20 years preceding the rash she had been receiving guanethidine and a monosulfamyl diuretic for hypertension. Guanethidine was suspected as causing the skin rash and was stopped but the rash continued. In 1977, a diagnosis of Sézary syndrome was made. Years before, she recalls a doctor telling her never to take sulfonamide again after it made her very "sick." We performed patch tests to guanethidine and monosulfamyl (a long-acting sulfonamide) which were negative and positive respectively.

Case 3.—A 53-year-old white male had a "nervous breakdown" in 1973 and was prescribed piperazinyl phenothiazine. In June 1976, a rash developed in the creases of the arms, knees, back, and forehead. Medication was stopped and the rash cleared except on the forehead. He began receiving diazepam and amitriptyline hydrochloride. In October 1976, the rash spread to the feet and abdomen. All drugs were stopped. The rash did not clear. In January 1977, piperazinyl phenothiazine was resumed. After seven tablets his lips turned a reddish purple and his throat became swollen. The drug was discontinued. The rash continued to spread and by November he had a generalized erythroderma. A diagnosis of Sézary syndrome was made in March 1977. The patient smoked 40 cigarettes a day for 32 years. He drank no alcohol. For 25 years he worked in a steel factory. He loaded steel pipes into the furnace; on entering the fire the pipes gave off strong fumes. Exposure to steel pipe fumes was calculated as 40 (hours a week) × 48 (weeks a year, 4 weeks a year off work) × 25 (years) = 48,000 hours over 25 years. After firing, an anticorrosive crude oil and water mixture was applied, so the patient's hands were wet all day. Crude oil exposure was similar to that of steel pipe fumes. The pipes were plated with tin. He was a skilled operator with tin and added acid and lead to the tinner machine. In addition, for 25 days a year he worked with "rustband"; his hands soaked in it 8 hours a day. Exposure to "rustband" was 25 (days a year) × 8 (hours a day) × 25 (years) = 5000 hours over 25 years.

TABLE 1.—Incidence of exposure of 44 CTCL patients to 4 agent subgroups*

Agents	No. of patients exposed	%
Chemicals	40	91
Drugs	38	86
Physical agents	9	20
Allergens	8	18

*All patients were exposed to > 1 agent. Individual agents are listed in the text.

Case 4.—A 55-year-old white male worked for a chemical company. For 1½ years (1950–1952) he stood by a vat distilling dichlordiphenyltrichloroethane (DDT). We estimated that he had approximately 3000 hours of exposure over 1½ years. For 3½ years he was exposed to lethane, sulfuric acid, and myriatic acid for approximately 6000 hours. In 1956, a bald spot appeared on his scalp and slowly spread until his face, arms, legs, and trunk were involved. The face and scalp had the largest lesions; these were the areas of maximal exposure to the chemicals. In 1978, a diagnosis of alopecia mucinosis and mycosis fungoides was made.

All but one of the 44 patients were exposed to more than one agent. The percent incidence of exposure at onset of the skin disease is shown in table 1. In four of the 44 patients, no chemical exposure was found. Only one of the 39 patients questioned had no drug exposure. The mean duration of exposure was 13 years (range, 1–50 years) for chemicals, 18 years (range, 2–48 years) for drugs, and 15 years (range, 9–30 years) for allergens.

The most frequently observed agents in each category are shown in table 2. In the subset of chemical agents 39% of the patients had been exposed to air pollutants (ten of 17 from chemical and processing factories near residences), 36% to pesticides, 30% to solvents and vapors, and 14% to detergents and disinfectants. Drugs were distributed as follows: tobacco, 86% (data for 32 patients only); analgesics, 20%; tranquilizers, 18%; and thiazide diuretics, 14%. Physical agents were radiation, 18%; therapeutic radiation (cobalt 60), 4%; and diagnostic or occupational radiation, 11% (eg, one technician worked 4–5 feet from the X-ray tube in the same room, without lead shielding protection). Allergens were bacteria (9%), mold and pollen (5% each), and house dust (2%) (patients had previous positive intradermal skin tests to mold, pollen, and house dust). Table 3 shows a 16-patient sample of the 44 CTCL patient series with multiple exposures to chemical and/or physical agents.

The range of chemical exposure was 2–201,600 hours. The chemicals involved (table 2) were as follows: (*a*) air pollutants from factories near residences (chemical, spice, candy, paper mill, laminated paper, plastic, and coal mine burning soft coal) and dust from textiles, permanent press fabrics, rug lint, steel mill, and coal factories; (*b*) pesticides including agent orange, DDT, chlordane, diazinon, pyrethrum, malathione, carbamate, and agricultural and corn pesticides; (*c*) solvents and vapors (methane, high octane fuel, gasoline, carbon tetrachloride, chemicals for rug production including dyes, paint thinner, methyl chloride, lethane, acetylene, ethylene, creosote, turpentine, and kerosene); (*d*) soap, disinfectant, detergent, and bleach; (*e*) metals (mercury, arsenic, chromium, copper, selenium, and lead in paint and in steel plating); (*f*) photographic chemicals; (*g*) plastics (methyl methacrylate); (*h*) hair beauty products (permanent waving thioglycolate, hair color rinse, and paraphenylenediamine); (*i*) asbestos; and (*j*) miscellaneous including one each of potash, lime, yarn chemicals, black dye, methyl salicylate, *p*-aminobenzoate ("Coppertone," a sunscreen which produced an acute contact dermatitis and the skin never cleared), and phosphorus. The majority of patients continued to be exposed to the agents for years after the clinical disease began. There was a trend toward a decrease of early stage disease as duration of chemical exposure increased. Only in stage V patients did the disease seem to increase with increased exposure.

In our patients, exposure to chemicals that are carcinogens included the following: polycyclic aromatic hydrocarbons, benzopyrene (soft burning coal,

TABLE 2.—% of patient exposure to the most frequently encountered agents*

Chemical	% exposure	Drug	% exposure	Physical agent	% exposure	Allergen	% exposure
Air pollutants	39	Tobacco	86	Radiation	18	Bacteria	9
Pesticides	36	Analgesics	20	Burns	2	Mold	5
Solvents and vapors	30	Tranquilizers	18			Pollen	5
Detergents and disinfectants	14	Thiazides	14			House dust	2

*This table lists the most common items in each agent subset and the % incidence of each item in the total patient population of 44. All patients were exposed to > 1 agent. Individual agents are listed in the text.

TABLE 3.—16-patient sample among the 44 CTCL patients with multiple exposures to chemical and/or physical agents

Patient No.*	Age/race/sex	Disease†		Stage	Onset of disease	Exposure to chemicals and/or physical agents	Total exposure	
		MF	SS				Hrs	Yrs
1	67/W/M		+	IV	1968	Colloidal gold 198 given for unknown reason in 1967	—	—
2	51/W/M	+		IV	1972	Refrigerant engineer with multiple exposures to:		
						Methyl chloride, freon 12, and methane	58	21
						Carbon tetrachloride	3	4
3	36/AI‡/M	+		IV	1961	Creosote (exposure for further 4 yrs)	28	1
4	75/W/F	+		III	1958	House sprayed professionally monthly with chlordane (to which grandson was allergic), diazon, and pyrethrum	240	10
5	55/B/M		+	IV	1957	X-ray technician for 25 yrs; developed own films; rash began on leg after 5 yrs of radiation exposure	—	5
6	54/W/M		+	IV	1972	Truck driver for chemical firm for 6 yrs:		
						Rash began on face and chest after 2 yrs of handling cement, methylene, and potash (further 4 yrs of exposure)	520	2
						Weekly fluoroscopy of heart for 1 yr during childhood	—	1
7	73/W/F		+	IV	1972	Exposures to:		
						Paris green (arsenic) during childhood	24	4
						Kerosene (prolonged exposure)	1305	45
						Guanethidine and monosulfamyl	—	15
8	69/W/M	+		I	1952	Paris green (arsenic) exposure in childhood	176	4
9	40/W/M	+		I	1962	Employed in chemical factory handling crude petroleum products	1500	0.9
10	54/W/M		+	V	1976	Exposures from:		
						Applying anticorrosives, tin plating with lead and acid, and applying "rustband" (worked in steel factory loading pipes into furnace)	48,000	25
						Phenothiazine taken for nerves	—	3
11	49/W/M		+	IV	1969	Merchant marine exposed to:		
						Constant use of detergents	36,000	22
						Asbestos wrapping over bunk with gross asbestos dust	8000	5
12	54/W/M	+		IV	1967	Painter with exposure to:		
						Paint thinner	627	19
						Turpentine and lead-based paint	152	19
						Phosphorus (3rd degree burns from explosion)	—	—
13	53/W/F	+		II	1969	Hypernephroma, 1964; received cobalt radiation (4500 rads)	—	—
14	47/W/F		+	V	1971	Renal cell cancer, 1966; received cobalt radiation (4485 rads)	—	—
15	55/W/M	+		IV	1963	Exposures to:		
						Copper fragments in head and neck from shell explosion	131,040	15
						Methane, sulfuric acid, and myriatic acid (1947–1950) (chemical factory worker)	6000	3.5
						DDT (1950–1952)	3000	1.5
16	45/W/M	+		I	1969	Exposures from:		
						Working during summers in fiberglass factory	—	3
						Making dental plates with methyl methacrylate	2250	15

*See Results section for case reports of patients 3, 7, 10, and 15.
†MF = mycosis fungoides; SS = Sézary syndrome.
‡AI = American Indian.

tobacco smoke, and car exhaust), carbon tetrachloride, crude petroleum products, aniline dye, DDT (carcinogenic in rodents), inorganic chemicals including chromium (chromium salts in cement), lead (lead-based paint and lead in tin plating of steel), and arsenic (in Paris green insecticide), asbestos (insulation), and creosote.

The onset of disease in three patients began with a drug reaction after which the skin never cleared. The drugs implicated were dyrenium and hydrochlorothiazide, piperazinyl phenothiazine, and monosulfamyl. In each case of drug-induced disease, the CTCL was Sézary syndrome.

Of 28 patients questioned about smoking, 24 were smokers and four were nonsmokers. The mean duration of smoking was 24 years (range, 5–43 years) with a mean of 25 cigarettes per day. Fourteen of 22 patients questioned had recurrent herpes simplex.

A preceding carcinoma occurred in two women; both had had renal cell carcinoma treated by nephrectomy and cobalt 60 radiation. In both cases CTCL developed 5 years after therapy. In addition, one man had a basal cell epithelioma of an ear 1 year after diagnosis of CTCL and one woman also had a basal cell epithelioma of an ear.

A family history of carcinoma occurred in 11 patients of whom six had one family member affected with a total of 20 cancers. Cancers were leukemia (four cases), uterine cancer (four), gastric cancer (three), pulmonary cancer (two), squamous cell carcinoma (of the lip in one patient and the face in one), pancreatic cancer (two), vocal cord cancer (one), colon cancer (one), and prostatic cancer (one).

DISCUSSION

In view of the limitations of this study, the absence of a control group, and the relatively small size of the test population, the results must be considered tentative. The following observations seem consistent with the etiologic role of exposure to chemicals and certain host factors in CTCL, and seem to justify a controlled investigation on a larger patient population. A history of exposure to multiple agents, at the time of onset of the skin eruption, was found by taking detailed histories from all but one of 44 CTCL patients in the test series. Two patients worked in chemical factories and seven patients lived near chemical factories. There had been uninterrupted continuity between agent exposure, onset of skin disease, and CTCL in all cases except those with exposure to radiation and DDT. In patients with CTCL the incidence of systemic disease tended to increase with the amount of exposure. A number of the chemicals to which patients were exposed are known carcinogens. The mean duration of exposure to chemicals was 13 years. This is in keeping with the long latency of chemical carcinogenesis.

The following observations with possible relevance to the etiology of CTCL were also made. Cancer in family members was found in 11 patients, including four cases of leukemia. Family susceptibility to cancer is known (17). Second primary cancers were also found in two patients. They are a known feature of carcinogenesis (18). In the two women who received cobalt radiation for renal carcinoma, CTCL began 5 years after radiation in each case. One of these patients had a leukemic form of CTCL. Leukemia is a post-radiation complication with a latent period of 5 years (16). Fourteen of 22 patients had recurrent herpes simplex. Southam et al (23) found that an antecedent or existing viral infection with a specific non-oncogenic virus may potentiate the effect of chemical carcinogens.

The results reported here suggest that patients with chronic skin disease are likely candidates for developing CTCL if they show long-term exposure to chemicals and/or drugs, long-term heavy smoking, or recurrent herpes simplex. In dealing with chronic skin diseases it would seem worthwhile to take a detailed history of agent exposure until our work is confirmed or disproved. If unusual agent exposure, particularly to carcinogens, is found, the patients should be followed closely and consideration should be given to removing the patients from the exposure.

It is not known whether the disease may result from chronic irritation by persistent antigens (10) which could reach the skin externally from the environment or internally as iatrogenic drugs. If, however, the persistent antigen in the skin was a carcinogen, as in our case of creosote and other exposures, or if persistent antigen and a carcinogen or co-carcinogen were both present, mutagenesis may occur with the evolution of CTCL.

Although this relatively small uncontrolled series does not prove a causal connection between exposure and CTCL, the presence of exposure in all 44 patients seems to indicate that the concept merits further exploration. This is now in progress at this center.

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Mycosis Fungoides: Epidemiologic Observations

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SUMMARY

An analysis of cases from a multi-hospital, pathologically verified clinical series and of deaths from US mortality statistics available at the county level for 1950–1975 (excluding 1972) was made in order to obtain information on the etiology of mycosis fungoides (MF). Despite the absence of an appropriate comparison group, the cases seemed to have a high frequency of antecedent allergies, fungal and viral skin infections, sun sensitivity, familial aggregation of lymphoma and leukemia, and employment in a manufacturing occupation (especially petrochemical, textile, metal, and machinery industries). The mortality survey revealed a predominance among males, nonwhites, and residents of the northeastern US, the latter due partly to an association between MF mortality and population size. The influence of occupational exposures was suggested by the excessive MF mortality rates in counties where petroleum, rubber, primary and fabricated metal, machinery, and printing industries were located.

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Mycosis fungoides (MF) is an uncommon cutaneous lymphoma of thymus-dependent lymphocytes. Its cause is obscure, and no systematic assessment of risk factors has been reported. In an effort to obtain etiologic clues, we evaluated data collected by the Mycosis Fungoides Cooperative Study Group (MFCSG) (1) and the county-by-county survey of cancer mortality conducted by the National Cancer Institute (NCI) (2).

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[3]We are grateful to Dr. Thomas Kubota, whose alert clinical observations prompted this survey, members of the Mycosis Fungoides Cooperative Study Group for providing the cases for analysis, Richard Ramsbottom, Boyd Stephenson, and B. J. Stone for assistance in data processing, Drs. Thomas J. Mason and William J. Blot for advice in study design and analysis, and Janet Bartch and Ruth E. Brounstein for technical assistance.

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MATERIALS AND METHODS

Mycosis Fungoides Cooperative Study Group

The MFCSG is a multi-institutional, interdisciplinary program which was established in 1972 to evaluate diagnostic procedures and therapy for MF (1). There are now 26 collaborating centers throughout the US. Although its primary focus is clinical, all patients referred for evaluation complete a standardized questionnaire which includes information on demographic, medical, familial, occupational, and evironmental variables. A computer file of these data was created and analyzed.

In order to evaluate the role of occupation and industry, a life-time occupational history was requested in the intake questionnaire. A code was assigned to each occupation held for > 1 year, based on a modification of the Industrial Classification System of the 1970 census (3). A special category of "repair and maintenance" was created to encompass occupational exposures which did not fit into the "manufacturing" category (eg, plumbers, electricians, service station operators, welders, etc). A category of "other" occupations included the remaining groups (eg, clerical, white collar, service,

and professional). Because some patients were employed in more than one occupation, the totals in this analysis are > 100%.

Of the 429 patients referred to the MFCSG for evaluation, 211 were designated as definitely having MF on the basis of review by the MFCSG Pathology Panel. The following analysis is restricted to this group of patients. Since an appropriate comparison group was not available, these data were evaluated qualitatively in order to generate etiologic hypotheses for subsequent analytic studies.

US Cancer Mortality by County

From all cancer deaths occurring in the geographically contiguous US between 1950 and 1975 (excluding 1972), those ascribed to MF in the International Classification of Diseases (code No. 205 in the 7th revision and No. 202.1 in the 8th revision) were identified. A computer file was created to include the sex, race, age and year at death, and county of residence for each case. Demographic data for each of the 3056 counties in the US were obtained from the 1960 census (4), including the population distribution by age, race, and sex, the total population, and the median school years completed by the adult population. The influence of urban environment on MF mortality rates was assessed by stratifying all counties into one of three population levels (< 25,000, 25,000–249,999, and ≥ 250,000) and cross-classifying this variable with others of interest. Similarly, the influence of social class was assessed by stratifying all counties into one of three education levels as measured by median number of school years completed (< 9 years, 9–10 years, and > 10 years).

Estimates of the number of employees engaged in each of the 18 major categories of industrial production, 2-digit Standard Industrial Codes (SIC) 21–38, were derived for each of the counties from the 1963 Census of Manufacturers (5). For each industry, the number of manufacturing plants per worker size-class (< 20, 20–49, 50–99, 100–249, 250–499, 500–999, and ≥ 1000 workers) was given by county. The total number of workers in that industry was estimated by multiplying the midpoint of each size-class (using 1500 as the midpoint of the final open size-class) by the corresponding number of units and summing over the units. The estimated number of employees in each manufacturing industry was divided by the total county population. The counties were then classified into three groups based on the percentage of the population employed: (*a*) < 0.1% (little or none); (*b*) 0.1%–1.0% (moderate); and (*c*) > 1.0% (high).

Age-, race-, and sex-specific annual MF mortality rates per million population were calculated for the 25-year period of 1950–1975 (excluding 1972) for each of the 3056 US counties. All rates were age-adjusted by the direct method, using the total US population in 1960 as the standard. Age-adjusted mortality rates were calculated for the five pentads and for groups of counties as determined by cross-classification of demographic and industrial variables. The expected number of MF deaths for each group of counties was determined by applying age-, race-, and sex-specific total US mortality rates to the corresponding populations and summing. Standardized mortality ratios (SMR) ([observed deaths divided by expected deaths] × 100) were calculated for each group of counties. Since there were so few MF deaths among nonwhite patients, detailed analyses were restricted to white patients. Because of the rarity of this neoplasm, tests of statistical significance were not applied.

Incidence Data

Incidence data for MF in the US during 1973–1976 were provided by the Surveillance, Epidemiology and End Results (SEER) program of the Biometry Branch, Field Studies and Statistics Program, Division of Cancer Cause and Prevention, NCI. The 11 participating cancer registries provide data from geographic areas representing 10% of the total US population.

RESULTS

Mycosis Fungoides Cooperative Study Group

General.—Table 1 reveals the distribution of MF cases by age, race, and sex. Age-specific incidence data from the SEER program are shown for comparison. The disease was predominant in males (85%) who were usually in the mid-adult years (64% were between 45 and 69 years of age). All but three nonwhite patients were black. Among patients reporting marital status, 75% were married, 14% were widowed, 7% were single, and 4% were divorced. The median number of school years completed was 12; 60% were high school graduates, including 34% with education beyond high school.

Personal medical history.—Specific information was available on childhood eczema, asthma, hay fever, urticaria, and allergies to food, drugs, or contact allergens. One hundred and eighteen of the MF patients (56%) reported at least one of these conditions, one half of whom had two or more (table 2). Fungal or viral infections of the skin were reported by 135 (64%) of the patients, with 28% reporting two or more such conditions (table 3).

TABLE 1.—Age at diagnosis by race and sex in MFCSG case series

Age (yrs)	No. (%) of— White males		White females		Nonwhite males		Nonwhite females		Totals		SEER incidence* (× 10^5)
25–29	4	(3.4)	2	(3.2)	0		1	(7.1)	7	(3.3)	–
30–34	2	(1.7)	0		2	(11.8)	1	(7.1)	5	(2.4)	0.1
35–39	3	(2.5)	4	(6.5)	1	(5.9)	1	(7.1)	9	(4.3)	–
40–44	9	(7.6)	7	(11.3)	0		2	(14.3)	18	(8.5)	0.1
45–49	24	(20.3)	8	(12.9)	2	(11.8)	0		34	(16.1)	0.2
50–54	15	(12.7)	10	(16.1)	5	(29.4)	2	(14.3)	32	(15.2)	0.1
55–59	10	(8.5)	6	(9.7)	1	(5.9)	4	(28.6)	21	(10.0)	0.3
60–64	13	(11.0)	9	(14.5)	2	(11.8)	1	(7.1)	25	(11.8)	0.5
65–69	14	(11.9)	4	(6.5)	4	(23.5)	1	(7.1)	23	(10.9)	0.6
70–74	11	(9.3)	6	(9.7)	0		1	(7.1)	18	(8.5)	0.4
75–79	5	(4.2)	4	(6.5)	0		0		9	(4.3)	0.5
80–84	4	(3.4)	0		0		0		4	(1.9)	0.4
85–89	1	(0.8)	1	(1.6)	0		0		2	(1.0)	–
Unknown	3	(2.5)	1	(1.6)	0		0		4	(1.9)	–
Totals	118		62		17		14		211		

*Average annual age-specific incidence of MF reported to the SEER program during 1973–1976, all races and sexes combined.

Antecedent noninfectious skin conditions were noted in 162 patients (77%). There were 35 patients (16%) with a possible MF precursor state (eg, parapsoriasis, poikiloderma, and alopecia mucinosa), and 38 patients (18%) with an atopic skin disorder. The most frequently reported diagnosis was "dermatitis, not otherwise specified," noted in 53 patients (25%). Ten patients reported another cancer prior to the diagnosis of MF: two patients each with cancers of the colon, prostate, and endometrium; two with lymphomas; and one each with thyroid and bladder cancer. Two patients reported cancers (lung carcinoma and multiple myeloma) following the diagnosis of MF. Previous surgical procedures in MF patients were recorded as follows: tonsillectomy, 39%; appendectomy, 29%; splenectomy, 4%; and thymectomy, 0.5%.

TABLE 2.—History of allergic conditions in MFCSG case series

Variable	No. of cases	%
Contact allergy	49	23.2
Urticaria	49	23.2
Drug allergy	46	21.8
Food allergy	21	10.0
Hay fever	21	10.0
Childhood eczema	12	5.7
Asthma	9	4.3
Negative history	93	44.1
Positive history	118	55.9
No. of allergic conditions		
1	60	28.4
2	32	15.2
3	21	10.0
4	5	2.4

Family history.—Skin disease was reported in a first-degree relative of 56 patients (26%) with MF. An affected parent was reported by 5% of patients. Most frequently noted was nonspecific dermatitis, followed by eczema. No precursor lesions to MF were reported. A history of cancer in a first-degree relative was reported by 63 MF patients (30%) with a parent affected in 42 patients (20%). Of special interest was the occurrence of lymphoma and/or leukemia in the first-degree relatives of nine patients with MF (fig 1). In family No. 1, MF developed in a father and a daughter.

Toxic exposures.—Patients were asked to report exposures to "hazardous chemicals or materials" (table 4). There were 63 patients (30%) who indicated at least one such exposure, especially to petrochemicals (11%), metals (7%), and solvents (6%). Information on route, frequency, and duration of exposure was not available.

Industry.—The majority of MF patients (59%) were employed in jobs belonging to the category of other industries, followed by 61 patients (29%) in

TABLE 3.—History of infectious skin disorders in MFCSG case series

Variable	No. of cases	%
Fungal	43	20.4
Herpes simplex	82	38.9
Warts	79	37.4
Negative history	76	36.0
Positive history	135	64.0
No. of skin infections		
1	75	35.5
2	51	24.2
3	9	4.3

TABLE 4.—Reported toxic exposures in MFCSG case series

Toxic exposure	No. of cases	%
Petrochemicals	23	10.9
Metals	14	6.6
Solvents	13	6.2
Particulates	9	4.3
Insecticides	8	3.8
Acids/alkali	8	3.8
Gases	6	2.8
Plastics	4	1.9
Miscellaneous	6	2.8
Patients reporting ≥ 1 toxic exposure	63	29.9

the manufacturing industries (table 5). Among the 46 males (34%) with manufacturing occupations, four worked in two different industries. The manufacturing primarily involved chemicals (11 patients; 5.2%), textiles and apparel (ten patients; 4.7%), and metals, nonelectrical machinery, and transportation equipment (eight patients each; 3.8%). No correlation was seen with the previously mentioned histories of toxic exposures.

Sunlight.—Fair complexion was reported in 48% of patients, ruddy skin in 18%, and dark skin in 24%. There were 90 patients (43%) who reported that they "burn easily" on sun exposure.

Multiple factors.—If one considers histories of allergic conditions or skin infections, family occurrences of cancer (in first-degree relatives), exposure to toxic substances, manufacturing occupation, and sun sensitivity as six possible risk factors, 18 patients (8%) had none, 168 (80%) had two or more, and 108 (51%) had three or more. Sun sensitivity, allergy, and previous skin infections seemed closely interrelated. For example, two thirds of all patients who "burn easily" also reported each of the other two factors.

US Cancer Mortality by County

General.—During the 25-year period of 1950–1975 (excluding 1972), there were 1948 deaths attributed to MF in the US: 1034 in white males, 631 in white females, 162 in nonwhite males, and 121 in nonwhite females. The average annual age-specific mortality rates revealed consistently higher mortality rates among males than females and among nonwhites than whites (fig 2). The mortality rate rose sharply with age, peaking at 65–69 years for nonwhite males and at 75–84 years for white males. The average annual age-adjusted mortality rates for the US during this 25-year period were as follows: white males, 0.53×10^6; white females, 0.28×10^6; nonwhite males, 0.84×10^6; and nonwhite females, 0.54×10^6. The average annual age-adjusted incidence rates for the 11 SEER cancer registries during 1973–1976 were: white males, 0.2×10^5; white females, 0.1×10^5; black males, 0.3×10^5; and black females, 0.1×10^5 (SEER program, unpublished data).

Time trends.—The average age-adjusted mortality rates by race and sex by pentad revealed a generally upward trend over time (fig 3). Mortality rates rose 10%–20% between the first and last pentads for whites of both sexes and nonwhite females while the rate doubled for nonwhite males. Inconsistencies in these patterns are probably due to small numbers, particularly in nonwhites.

Geographic and demographic patterns.—The MF mortality rate was highest among white males in the northeastern US (0.61×10^6), with an SMR of 115. The remaining three geographic regions (south, central, and west) had similar mortality rates (ranging from 0.49 to 0.53×10^6) and SMRs near 100. Deaths among white females were uniformly distributed. In general, the MF mortality rate rose

TABLE 5.—Reported occupational history in MFCSG case series

Occupational category	No. (%) of—* All males		White males		Nonwhite males		White females		Nonwhite females		Totals	
Manufacturing	46	(34.1)	41	(34.7)	5	(29.4)	15	(24.2)	—	—	61	(28.9)
Repair/maintenance (machinery)	28	(20.7)	24	(20.3)	4	(23.5)	—	—	—	—	28	(13.3)
Construction	13	(9.6)	11	(9.3)	2	(11.8)	—	—	—	—	13	(6.2)
Agriculture	13	(9.6)	12	(10.2)	1	(5.9)	1	(1.6)	—	—	14	(6.6)
Mining	6	(4.4)	6	(5.1)	—	—	1	(1.6)	—	—	7	(3.3)
Other	67	(49.6)	57	(48.3)	10	(58.8)	45	(72.6)	13	(92.9)	125	(59.2)
Unknown	5	(3.7)	4	(3.4)	1	(5.9)	8	(12.9)	1	(7.1)	14	(6.6)
Total work force	135		118		17		62		14		211	

*Percents add up to > 100 because of individuals with > 1 occupation.

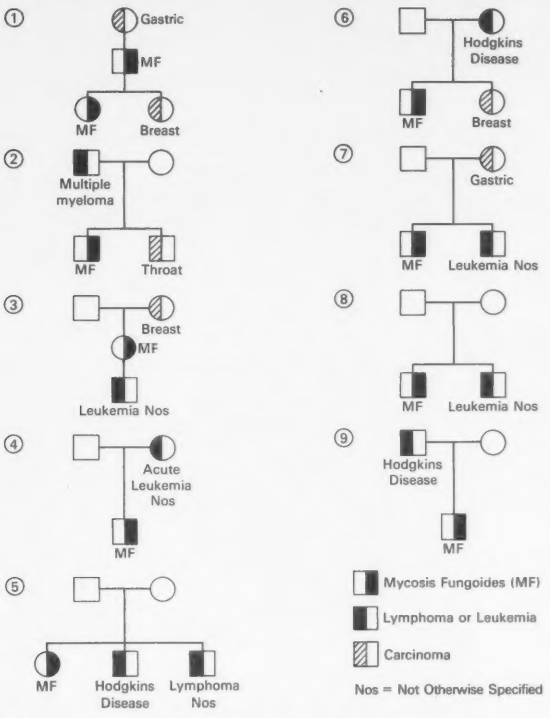

FIGURE 1.—Pedigrees of 9 families from the MFCSG case series in which leukemia and/or lymphoma was reported in a first-degree relative of an MF patient.

among white males as the population increased, a pattern observed in all four geographic regions (table 6). The highest rates were observed in the northeast for counties whose populations were ≥ 250,000 (SMR = 123). White females had no clear overall pattern, although there was a trend towards higher rates with increasing population in the south and central US. The northeastern and urban predominance among white males is shown also by mapping MF mortality by county (fig 4). Every county with at least one death is shaded in, with counties having at least two deaths *and* an SMR of > 150 highlighted in black. The pattern of MF mortality rates by level of education was inconsistent in white males, both nationally (where the middle level of education had the highest rate) and regionally (table 7). Among white females, the mortality rates rose slightly with the level of education nationally and in three of the four geographic regions. Cross-tabulation of mortality rates by population and education in white males revealed that the rates were similar within a given population category as the education level increased, but that rates rose within each education level as population increased.

Industry.—In view of the small number of deaths reported, a positive correlation between MF deaths and a specific industry was accepted only if (*a*) there was a stepwise gradient in the mortality rate from lowest to highest level of employment, (*b*) the gradient in the mortality rate was observed in at least three of the four geographic regions, and (*c*) the SMR was > 110 for the highest level of employment. The strongest association was noted for the petroleum industry (table 8). The SMR was 160 for those counties with > 1.0% of their populations employed in the manufacture of petroleum products. This pattern was observed both in white males and females. The northeast, south, and west had positive mortality gradients in males, while all four regions showed a positive gradient for females. A positive correlation was observed between MF mortality, among white males only, and the manufacture of rubber, primary metals, fabricated metals, machinery, and printing. A correlation was also seen with the manufacture of scientific instruments and photographic equipment, but was limited to one geographic region. In order to define these industrial associations more precisely, 4-digit SIC codes were analyzed for those counties with > 1% of their population employed in any of the six industries noted above in which there were also at least two MF deaths and an SMR of > 150. The specific subgroups noted most frequently within the six "suspect" industries were as follows: *printing*—newspaper and commercial printing; *petroleum*—petroleum refining; *rubber*—manufacture of fabricated rubber products and miscellaneous plastic products; *primary metals*—blast furnaces, steel mills, and foundries and the rolling, drawing, extruding, and casting of nonferrous metals; *fabricated metals*—manufacture of bolts, nuts, screws, rivets, valves, and pipefittings; and *machinery*—manufacture of farm and construction equipment. The male-to-female ratio of mortality rates was evaluated by industry on the assumption that a rising ratio with increasing levels of employment might imply work-related exposures, since males dominate the manufacturing workforce by a ratio of three to one (6). Generally, the sex ratio varied between 1.8 and 2.0 for most industries. In the following industries a modest rise in sex ratio was observed: paper (1.6 to 2.7), rubber (1.8 to 2.6), textiles (1.9 to 2.4), apparel (1.7 to 2.1), and printing and chemicals (both 1.9 to 2.3).

MYCOSIS FUNGOIDES: AGE-SPECIFIC MORTALITY RATES FROM COUNTY RESOURCE

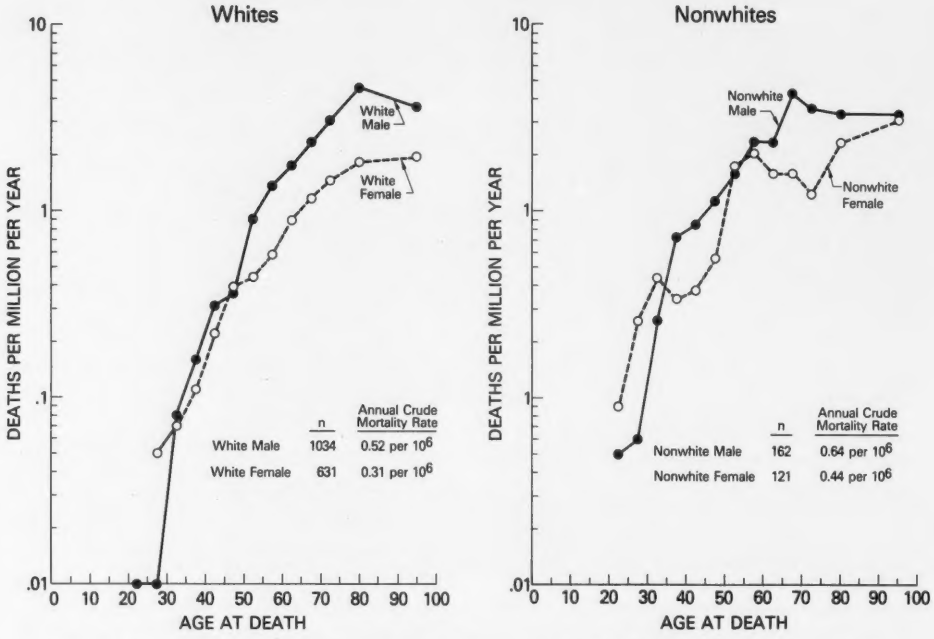

FIGURE 2.—Average annual age-specific MF mortality rates in the US during 1950–1975 (excluding 1972) by race and sex.

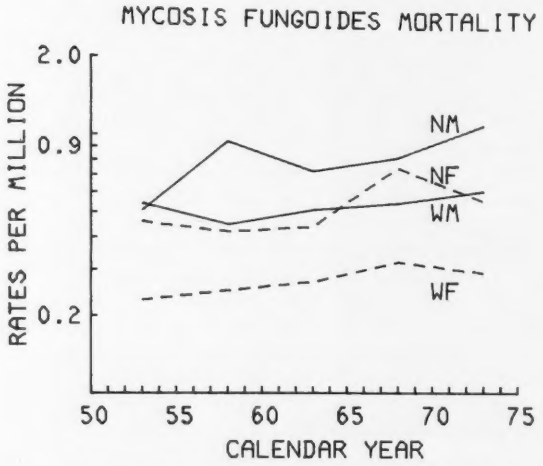

FIGURE 3.—Average annual time-period-specific MF mortality rates in the US during 1950–1975 (excluding 1972) by race and sex. Rates were calculated for each of 5 pentads: 1950–1954, 1955–1959, 1960–1964, 1965–1969, and 1970–1975 (excluding 1972).

DISCUSSION

The cutaneous origin of MF has raised suspicions that direct environmental exposures might be involved in its pathogenesis. One hypothesis has linked MF to epidermal Langerhans' cells (7), which play a role in the primary immune response to external contact antigens (8–11). This model suggests that Langerhans' cells modulate the response of specific T lymphocytes to various foreign antigens; persistence of these substances in the skin may lead to chronic antigenic stimulation, which in turn can produce lymphoproliferative malignancy in laboratory animals (12) and possibly in man (eg, following renal transplantation). The influence of environmental agents on MF may be supported by the affinity of Langerhans' cells for such contact sensitizers as heavy metals (eg, mercury, nickel, and chromium) and various aldehydes and amines (9).

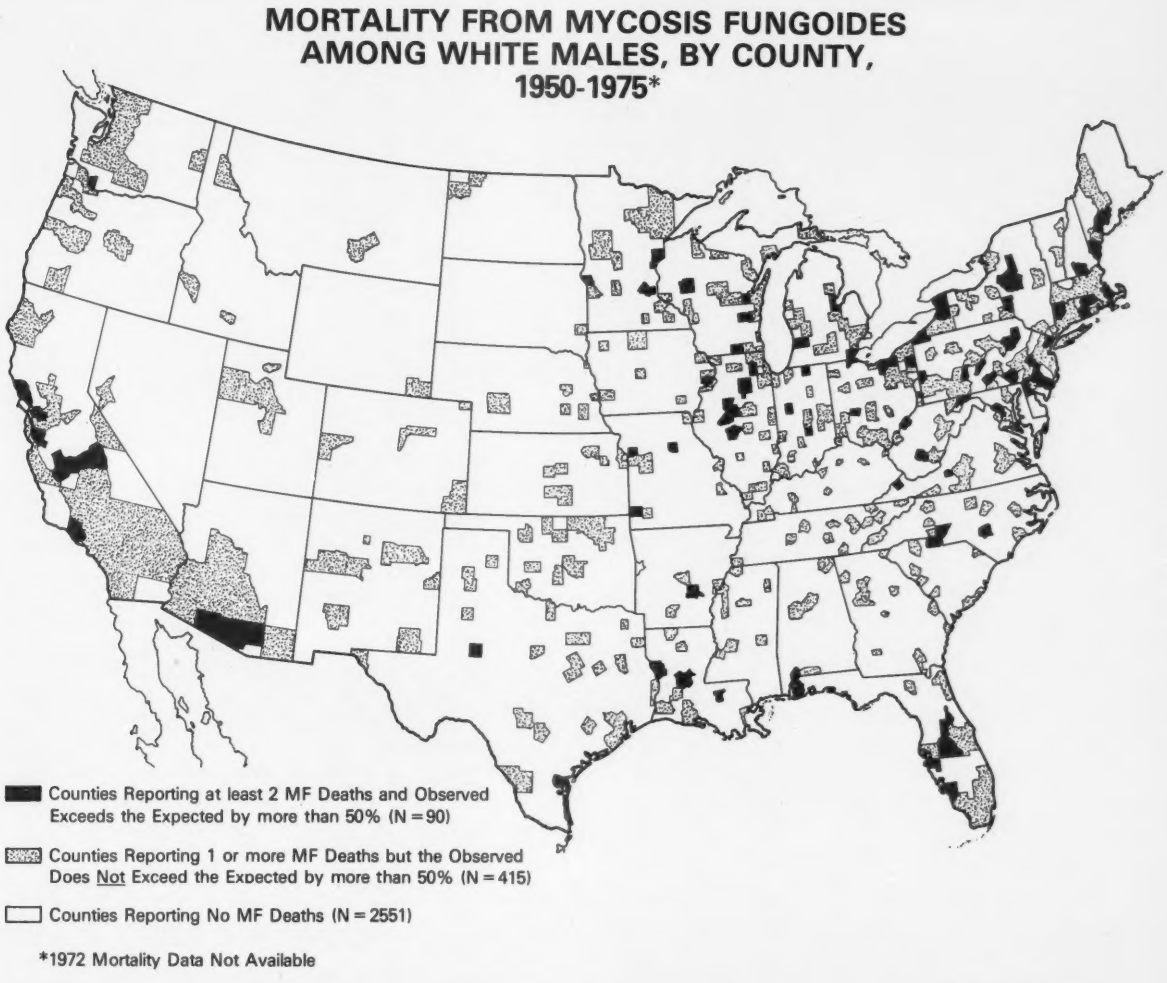
MORTALITY FROM MYCOSIS FUNGOIDES
AMONG WHITE MALES, BY COUNTY,
1950-1975*
Counties Reporting at least 2 MF Deaths and Observed Exceeds the Expected by more than 50% (N = 90)
Counties Reporting 1 or more MF Deaths but the Observed Does Not Exceed the Expected by more than 50% (N = 415)
Counties Reporting No MF Deaths (N = 2551)
*1972 Mortality Data Not Available

FIGURE 4.—MF deaths among white males in the US during 1950–1975 (excluding 1972) by county. Each county in which ≥ 1 death occurred is shaded; counties with ≥ 2 deaths *and* an SMR of > 150 are highlighted in black.

TABLE 6.—MF mortality by region and population; white patients only

Region	Population level											
	< 25,000				25,000–249,999				≥ 250,000			
	Observed	Expected	SMR†	Rate*	Observed	Expected	SMR	Rate*	Observed	Expected	SMR	Rate*
						Males						
Northeast	1	3.2	31	0.17	84	85.0	99	0.53	238	193.8	123	0.66
South	50	66.9	75	0.40	118	125.4	94	0.50	83	78.1	106	0.57
Central	46	69.2	66	0.35	128	131.8	97	0.51	126	118.4	106	0.57
West	17	19.9	85	0.53	38	47.8	79	0.42	105	96.3	109	0.58
Totals	114	156.2	73	0.39	368	390.1	94	0.50	552	486.7	113	0.61
						Females						
Northeast	2	1.9	105	0.30	52	51.8	100	0.27	127	124.1	102	0.28
South	24	37.8	63	0.18	79	77.2	102	0.28	54	51.5	105	0.29
Central	25	37.3	67	0.19	82	78.4	105	0.30	89	74.4	120	0.33
West	9	8.2	110	0.29	26	26.6	98	0.27	62	61.8	100	0.28
Totals	60	85.1	71	0.20	239	234.1	102	0.28	332	311.8	107	0.29

*Average annual age-adjusted mortality rate/million.
†SMR = standardized mortality ratio.

TABLE 7.—MF mortality by region and education*: white patients only

Regi	Education level											
	< 9 yrs				9–10 yrs				> 10 yrs			
	Observed	Expected	SMR‡	Rate†	Observed	Expected	SMR	Rate†	Observed	Expected	SMR	Rate†
						Males						
Northeast	69	54.8	126	0.67	166	130.0	128	0.68	88	97.2	91	0.48
South	112	149.5	75	0.40	59	55.9	106	0.55	80	65.1	123	0.65
Central	69	83.9	82	0.43	111	113.7	98	0.51	120	121.9	98	0.53
West	5	4.7	106	0.53	14	16.8	83	0.45	141	139.6	101	0.53
Totals	255	292.9	87	0.46	350	316.4	111	0.59	429	423.7	101	0.54
						Females						
Northeast	29	34.3	85	0.23	81	80.6	101	0.28	71	62.9	113	0.31
South	76	89.2	85	0.24	37	35.8	103	0.28	44	41.5	106	0.30
Central	38	46.4	82	0.23	73	68.0	107	0.30	85	75.7	112	0.31
West	4	2.4	167	0.47	7	8.8	80	0.21	86	85.4	101	0.28
Totals	147	172.3	85	0.24	198	193.2	103	0.28	286	265.5	108	0.30

*Median No. of school yrs completed by adult population.
†Average annual age-adjusted mortality rate/million.
‡SMR = standardized mortality ratio.

TABLE 8.—MF mortality by industry and employment level: white males

Industry	Employment level					
	< 0.1%		0.1%–1.0%		> 1.0%	
	SMR†	Rate*	SMR	Rate*	SMR	Rate*
Petroleum	97	0.52	116	0.62	160	0.83
Rubber	94	0.50	106	0.57	129	0.68
Primary metals	90	0.48	105	0.56	117	0.63
Fabricated metals	87	0.46	98	0.52	115	0.62
Machinery	88	0.47	95	0.51	114	0.61
Instruments	90	0.48	116	0.62	126	0.67
Paper	83	0.44	112	0.60	118	0.63
Printing	90	0.48	97	0.52	118	0.63
Chemicals	83	0.44	110	0.59	115	0.61
Tobacco	100	0.53	104	0.56	97	0.50
Textiles	93	0.49	114	0.61	116	0.62
Apparel	93	0.49	102	0.54	106	0.57
Lumber	107	0.57	96	0.51	89	0.47
Furniture	93	0.50	108	0.57	91	0.49
Leather	97	0.52	115	0.61	88	0.47
Stone/glass	104	0.55	102	0.54	68	0.37
Electrical	87	0.46	111	0.60	103	0.54
Transport	95	0.51	99	0.53	116	0.62

*Average annual age-adjusted mortality rate/million.
†SMR = standardized mortality ratio.

Etiologic studies of MF have been rare. Familial susceptibility has been suggested by reports of four families with two or more cases of MF (13–16), but details were sparse. In the most recent of these reports (16), a family history of malignancy was equally frequent in a series of 48 MF patients and matched controls. Our study reports a fifth MF-prone family, plus the development of lymphomas or leukemias in eight additional families, suggesting that, in some instances, MF may be part of a familial predisposition to lymphoproliferative tumors. Genetic factors have also been suggested by the excessive frequency of the H–LA antigens, B8, Aw31, and Aw32, in MF patients (17). Sun sensitivity was present in a high proportion of cases, but the absence of a latitudinal gradient in the MF mortality rate suggests that the effect of sunlight is different from that seen with skin carcinomas and melanomas. The role of toxic exposures, suggested by our study, is in accord with anecdotal case reports of MF following exposure to irradiation, arsenic, bismuth, and tar ointments (18). Our clinical series of MF also suggested occupational factors consistent with an unpublished survey showing an excess risk among workers in the manufacturing and construction industries (16). A viral influence has been suggested by experiments in which extracts of human MF tumor cells produced lymphomatous infiltrates in mice (19), but these findings have not been confirmed.

In the absence of a control group, it is very difficult to interpret the results of the clinical series, but the following characteristics were felt to occur often enough to merit detailed evaluation in subsequent analytic studies: (*a*) history of allergic conditions; (*b*) history of fungal and viral skin infections; (*c*) family history of malignancy (particularly leukemia and lymphoma); (*d*) sun sensitivity; (*e*) exposure to toxic substances; and (*f*) a manufacturing occupation (especially in the petrochemical, textile, metal, and machinery industries).

The US cancer mortality data, analyzed after the clinical series, showed a positive geographic correlation between MF mortality rates and the proportion of white males employed in the petroleum, rubber, metal, machinery, and printing industries, a pattern similar to that seen in the clinical series. These associations were noted consistently in three of the four geographic regions studied. Furthermore, the male predominance in MF and the tendency for the sex ratio to rise with increasing levels of employment in some industrial areas are consistent with an occupational component in the development of MF. It should be noted that industry-specific groups of counties were not mutually exclusive; a given county might have large numbers of workers in multiple industries. The small number of MF deaths precluded separating possible interactions between industries. Caution must be exercised in interpreting these data, and associations should

be regarded as suggestive, not definitive. However, the results are consistent with findings from the clinical series and an unpublished report (16) linking MF to manufacturing industries.

The correlation of MF mortality rates among white males with population density suggests an increased risk associated with urban areas, but this pattern may be affected by referral of MF patients to treatment centers found in urban locations. The excess mortality rate noted for the northeastern US could not be explained entirely by industry or socioeconomic patterns, and may be related to the correlation with population density.

In summary, in an effort to identify candidate risk factors for MF, data were analyzed from a large, pathologically verified series of cases and from a nationwide mortality series. Case-control interview studies should be undertaken to pursue the clues generated by this survey, including the role of immunologic, genetic, industrial, and other environmental factors.

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Current Concepts in Immunoregulatory T-Cell Neoplasms

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SUMMARY

Normal T cells play a crucial role in the regulation of humoral immune responses by acting as potentiators (helper cells) or inhibitors (suppressor cells) of the B-cell transition into immunoglobulin-secreting plasma cells. Certain patients with leukemias or lymphomas of T-cell origin may provide a resource for obtaining homogeneous populations of cells which act as either helper cells (eg, some but not all patients with Sézary's syndrome) or suppressor cells (eg, some patients with acute or subacute T-cell leukemia). The clinical and theoretic implications of such immunoregulatory cell neoplasms are discussed.

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Although T cells may express antigen-binding receptors which have the same, or at least very similar, variable regions as the variable regions structurally linked with immunoglobulin heavy chains (1), normal T cells do not produce conventional immunoglobulins. However, T cells do play a critical role in the regulation of humoral immune responses by acting as potentiators or inhibitors of the B-cell transition into immunoglobulin-secreting plasma cells. Those regulatory cells that potentiate this B-cell transition are classified as helper cells, whereas those cells which inhibit this transition are classified as suppressor cells. Both antigen-specific and -nonspecific T-cell regulatory control exists (2). Accessory cells which belong to the monocyte-macrophage series are also extremely important in a wide range of regulatory T-cell to B-cell and also T-cell to T-cell interactions.

A number of important insights into the nature of the humoral response in man were made possible by studying neoplasms of the B-cell/plasma-cell series. The recognition that so-called paraproteins derived from patients with multiple myeloma represent extremely homogeneous immunoglobulins was an indispensable step in understanding the structural, functional, metabolic, and genetic aspects of humoral immunity. Malignancies of T-cell origin are of exceptional interest because in some instances the neoplastic T cells may retain immunoregulatory properties. For this reason, the study of malignant T cells and their products could eventually be as rewarding in resolving questions regarding cellular immunity, and especially the cellular control of immunoglobulin production, as myeloma and its paraprotein products have proved to be in resolving questions concerning humoral immunity. In this paper, we shall describe the use of neoplastic T cells from a variety of patients as a resource in studying human helper and suppressor T-cell function.

IN VITRO METHODS FOR THE STUDY OF HUMAN HELPER AND SUPPRESSOR CELL ACTIVITY

Measurement of Immunoglobulin Synthesis by Lymphocytes In Vitro

To study the transition of circulating lymphocytes into immunoglobulin-secreting plasma cells under conditions of polyclonal activation, lymphocytes were cultured in the presence of pokeweed mitogen for a period of 7–12 days. At the termination of the culture period, the amount of IgM, IgG, and IgA secreted into the media was measured using heavy

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chain-specific double antibody radioimmunoassays. This in vitro model has been described in detail previously (2,3). There are other polyclonal activators for human immunoglobulin production in vitro (eg, a water-soluble extract from *Nocardia opaca* and Epstein-Barr virus), but these agents probably behave differently from pokeweed mitogen, which is a highly T-cell-dependent lectin (*see* below).

Preparation of Normal T- and B-Cell Populations

Many of the studies described in this paper required B cells which were rigorously depleted of T cells. We prepared T cells and populations of B cells freed of T cells by a two-step procedure that takes advantage of the observation that normal T cells pass through anti-$F(ab')_2$ immunoabsorbent columns and form spontaneous rosettes with sheep red blood cells (SRBCs). On the other hand, normal B cells are selectively retained by immunoabsorbent columns (from which they may be eluted) because of their surface-bound immunoglobulin molecules, and do not form spontaneous rosettes with SRBCs. These methods were described in detail previously (4).

Assays of Helper Cell Activity

As previously mentioned, pokeweed mitogen is a T-cell-dependent polyclonal stimulator of immunoglobulin secretion. In operational terms, this means that pokeweed mitogen-stimulated human B cells, rigorously freed of T cells, secrete only very small quantities of immunoglobulin. The ability of added cells to augment immunoglobulin secretion by such normal B cells may be used as a test for helper activity (4,5). This is a test for antigen-nonspecific helper function. Unlike certain antigen-specific helper-cell assay systems in rodents, the pokeweed mitogen-driven helper-cell assay system does not exhibit histocompatibility restrictions.

Assays of Suppressor Cell Activity

The presence of suppressor cells was detected by a co-culture technique. Circulating cells from patients undergoing study and circulating lymphocytes from normal subjects were co-cultured together in the presence of pokeweed mitogen (3). The secretion of the immunoglobulin by cells from the two normal subjects in co-culture was related to the sum of the expected contribution by each cell population alone. IgM, IgG, and IgA production by mixtures of allogeneic lymphocytes from normal subjects ranged from 95% to 106% of the expected values. We considered a depression of immunoglobulin production in the co-culture system to $< 50\%$ of the expected value to represent a suppressor-cell effect. This assay is a test for antigen-nonspecific suppressor function.

HELPER CELL NEOPLASMS

Sézary's Syndrome

The Sézary's syndrome, as discussed elsewhere in this issue, is a serious disorder characterized by an exfoliative erythroderma, generalized lymphadenopathy, and circulating malignant lymphocytes with a propensity to infiltrate epidermis. These circulating neoplastic lymphocytes (referred to as Sézary cells) have a deeply folded (or cerebriform) nucleus as their dominant morphologic feature. In the epidermis, the neoplastic cells may form distinctive nests known as Pautrier's microabscesses. Skin biopsies from patients with Sézary's syndrome are essentially indistinguishable from those of patients with mycosis fungoides (MF). Based on the capacity to form spontaneous SRBC rosettes and susceptibility to lysis in the presence of complement and heterologous antisera raised against thymic lymphocyte antigens, Sézary's cells from most patients studied are thought to have a T-cell origin.

Most investigators would now agree that Sézary's syndrome is not truly a separate entity, but rather a clinical variant of MF. Overt transitions between these two entities are common. MF and Sézary's syndrome fit into the same spectrum of disease in terms of clinical, histologic, cytologic, and immunologic presentation. For many purposes it is extremely useful to consider these entities as comprising a unified cutaneous T-cell syndrome. At many medical centers, those patients with cutaneous T-cell lymphoma who have easily detectable circulating neoplastic lymphocytes would be classified as having Sézary's syndrome. Conversely, if no leukemic cells are observed, the diagnosis would be MF.

In 1966, Blaylock et al (6) provided the first suggestion that some patients with cutaneous T-cell lymphomas might have a neoplasm which represents an expansion of cells with immunoregulatory function. These investigators observed that many patients, with what would now be termed a cutaneous T-cell lymphoma syndrome, had exceedingly high serum levels of IgA. IgA is an important immunoglobulin which is found both in serum and external secretion. There is a large body of data to suggest that those B cells which ultimately mature into IgA-secreting plasma cells depend heavily on T-cell helper influence before final differentiation can occur (7). Thus, the striking elevation of a

highly thymic-dependent class of immunoglobulin (IgA) might have been the first clue that the neoplastic lymphocytes found in certain patients with cutaneous T-cell lymphoma had retained an important immunoregulatory function. Moreover, there have been reports of patients with Sézary's syndrome who developed monoclonal serum immunoglobulin abnormalities (8,9).[3] Conceivably, such examples of excessive B-cell activity could represent the in vivo expression of excessive helper T-cell function.

Results in our own laboratory over the past 3 years agree with the view that some (but not all) patients with the Sézary's syndrome variant of cutaneous T-cell lymphoma may have a disease that represents a homogeneous expansion of helper T cells. As previously discussed, normal human lymphocytes may be induced to produce immunoglobulins in vitro in the presence of pokeweed mitogen. The production of immunoglobulins by human lymphocytes in the presence of pokeweed mitogen is a T-cell-dependent process. In other words, highly purified normal human B cells will ordinarily not produce detectable levels of immunoglobulin in vitro unless helper T cells are also provided in this system.

It is worth emphasizing that stringent standards must be applied before a helper activity can be assigned to any given neoplastic population of cells. In some cases, indicator normal B-cell populations will produce normal (or nearly normal) quantities of immunoglobulin following stimulation with pokeweed mitogen in vitro when there is as little as a 2% contaminating population of normal T cells present. Therefore, in studying the helper activity of neoplastic lymphocytes a special effort to exclude the effects of contaminating residual normal T cells is necessary. In our studies of patients with Sézary's syndrome, we were able to select patients with extremely high T-leukemic counts. This provided us with a starting "biologic" purification. In addition, when the neoplastic lymphocytes of a patient appeared to mediate a helper effect (using an "undiluted" starting system for helper activity which involved 1.0×10^6 neoplastic T cells cultured with 5.0×10^5 normal indicator B cells), we studied the capacity of dilutions of the patients' cells to mediate "help" when co-cultured with normal B cells. We categorized the neoplastic cells as helper cells if they augmented pokeweed mitogen-driven normal B-cell immunoglobulin secretion using a ratio of five B cells to one T cell (5×10^5 normal indicator B cells in culture with 1×10^5 neoplastic cells).

[3]Fedou R. Personal communication.

Using the guidelines described above, five of 12 patients with Sézary's syndrome tested had peripheral blood neoplastic T cells which retained an in vitro helper activity. There was a sixfold to > 30-fold augmentation of immunoglobulin synthesis and secretion by normal B cells when co-cultured with Sézary cells derived from these patients. In addition, Sézary cells from one patient studied induced nearly a tenfold increase in IgA synthesis by lymphocytes obtained from a child with ataxia telangiectasia and isolated IgA deficiency. Moreover, these same Sézary cells induced a > 500-fold increase in IgA and IgG secretion by lymphocytes from a child with a severe congenital thymic deficiency (Nezelof's syndrome) (4). These studies cannot be explained on the basis of a simple allogeneic effect since the neoplastic Sézary cells which exerted the helper effect when co-cultured with lymphocytes from the child with ataxia telangiectasia and the child with Nezelof's syndrome neither stimulated nor responded in mixed leukocyte-reaction tests.

We recently studied a patient with Sézary's syndrome who developed an aggressive lymphoma, histologically classified as a T-cell immunoblastic sarcoma. Although these neoplastic cells formed spontaneous SRBC rosettes (and could thus be classified as having a T-cell origin), they did not have the typical cerebriform nuclei associated with Sézary cells, but rather, had round to oval nuclear contours. Nonetheless, these lymphomatous cells could mediate a helper T-cell function (5). We have also observed one infant with acute lymphoblastic leukemia who had neoplastic T cells which appeared to mediate a helper effect. (However, most patients with acute lymphoblastic leukemia do not have cells with detectable immunoregulatory activity.) These observations strongly suggest that neoplastic T cells from disease states other than Sézary's syndrome may eventually be found to mediate a helper-cell immunoregulatory activity.

SUPPRESSOR CELL NEOPLASMS

Subacute T-Cell Leukemia in Japan

Recently, the clinical and hematologic features of an apparently new kind of adult T-cell leukemia were described by Uchiyama and co-workers (10). This disease had several interesting features. It occurred in adults. There was generally a subacute leukemic course with a rapidly progressive terminal phase. The leukemic cells formed spontaneous SRBC rosettes and could be killed by heterologous antisera against human T-cell membrane antigens. Moreover, the leukemic T cells in this syndrome

frequently had lobulated nuclei (under electron microscopic examination, however, the nuclei were generally not as convoluted as those of typical Sézary's cells). There was frequent leukemic involvement of the dermis and subcutaneous layers; however, true epidermal infiltration and the formation of Pautrier's microabscesses, as might be seen in Sézary's syndrome, were distinctly unusual. Of note, lymphadenopathy and hepatosplenomegaly were common. None of the patients had mediastinal tumors, but approximately 25% showed significant parenchymal infiltration of the lungs.

Perhaps the most striking finding described by Uchiyama and co-workers was the geographic clustering of the patients' birth in the south of Japan. Thirteen of 16 patients reported were born in Kyushu, an island on which the city of Nagasaki is located. The role of atomic bombardment, and other environmental or genetic factors, in the epidemiology of this disease cannot be resolved at this time.

The leukemic T cells from three of six patients with this Japanese T-cell syndrome appeared to act as suppressor cells (11). That is, the leukemic cells inhibited immunoglobulin production by co-cultured normal lymphocytes in the presence of pokeweed mitogen. (Cytoplasmic immunofluorescence was used to determine immunoglobulin production.) Furthermore, supernatant fluids obtained from a short-term culture of leukemic cells of one of these three patients showed a marked suppressive effect on the capacity of normal lymphocytes to produce immunoglobulins. This supernatant fluid did not appear to mediate the suppressor effect through a mechanism of direct cytotoxicity. The suppressor effect was lost when the supernatant was heated at 56°C for 30 minutes. Thus, in contrast to the immunoregulatory capacity found in certain patients with Sézary's syndrome, patients with the Japanese form of subacute adult T-cell leukemia may have a neoplasm which originates from suppressor cells.

Acute Neoplastic Suppressor Cells From a Child With Acute Lymphoblastic Leukemia and Hypogammaglobulinemia

We recently studied an infant boy with acute lymphoblastic leukemia who had hypogammaglobulinemia at initial presentation (12). Since 55% of the leukemic cells formed spontaneous rosettes with SRBCs and were killed with a horse anti-thymocyte globulin plus complement, the neoplasm was classified as having a T-cell origin. One of the most striking features of this unusual child's disease was a profound depression of serum IgM and IgG concentrations. During treatment, the child received a number of drugs including hydroxyurea, vincristine, prednisone, daunorubicin, L-asparaginase, 6-mercaptopurine, methotrexate, and cyclophosphamide. The serum immunoglobulin levels rose during the course of treatment, and during the preterminal relapse of the leukemia there was once again a depression of serum IgM and IgG levels. When we first undertook our study of this patient, there were data that the hypogammaglobulinemia associated with a *subset* of patients with common variable immunodeficiency might be related to the presence of excessive suppressor T-cell activity (3). Since the leukemic infant had depressed serum immunoglobulin levels at the time of diagnosis, and also while his leukemia was in terminal relapse, we conducted tests to determine whether his circulating neoplastic cells could suppress the immunoglobulin synthesis of co-cultured normal lymphocytes. We observed that the neoplastic lymphocytes from the patient profoundly depressed immunoglobulin synthesis when cultured with equal numbers of lymphocytes from 11 normal subjects tested. The suppression of normal immunoglobulin generally ranged from 75% to 100% for the three classes of immunoglobulin (IgM, IgG, and IgA) tested. This neoplastic suppressor cell activity was nullified by prior exposure to 2000 rads of irradiation. The leukemic suppressor activity was a function of the number of neoplastic T cells added to normal lymphocytes, and suppression was observed with as few as one neoplastic cell to five normal cells for all three classes of immunoglobulin measured.

We then asked whether the patient's leukemic cells could mediate suppression by themselves or whether they required the presence of cooperating normal T cells. In mice, there are firm data to suggest that at least two different T-cell subsets may be required for the generation of so-called suppressor effector T cells (13,14). The data in mice support the hypothesis that a so-called prosuppressor (suppressor cell precursor) subset must interact with a so-called suppressor activator (suppressor "amplifier") subset before suppressor effector T cells can emerge.

We addressed the question of a possible requirement for T-T interactions by taking advantage of the relative radioresistance of normal helper T cells and the relative radiosensitivity of normal suppressor T cells. There are extensive data in mice, and corroborating evidence in man, to support this concept. Therefore, by the use of radiation immediately before culture it was possible to design experiments in which a T-cell population retains helper activity with minimal interference from cells which might in some way be engaged in suppressor cell activity. Accordingly, we measured immunoglobulin production by B cells plus irradiated normal T cells

in the presence of pokeweed mitogen. We reasoned that if the patient's circulating neoplastic T cells could mediate suppressor effects directly by themselves, they should be capable of inhibiting immunoglobulin production by normal B cells cultured with either irradiated or unirradiated normal T cells. On the other hand, if this patient's T cells had to interact with a cooperating subset of normal T cells before suppression could occur, they might be expected to depress immunoglobulin secretion only when unirradiated normal T cells were present. When we did these experiments, we found that in a pokeweed mitogen-driven system of immunoglobulin secretion, neoplastic T cells from the patient caused suppression only when unirradiated normal T cells were provided (12). In more recent experiments, we found that these neoplastic T cells appear to function as a population of prosuppressor T cells which can mature into suppressor effector T cells following interaction with a population of normal suppressor activator T cells (15). In some settings, the neoplastic prosuppressor T cells could mature into fully functional suppressor effector T cells under the influence of a soluble factor(s) secreted by cooperating normal T cells.

Based on our studies with these neoplastic prosuppressor T cells, we have constructed a general hypothesis for the induction of human suppressor effector cells. In this hypothesis, human suppressor T cells have an interim existence as prosuppressor cells. At this stage of maturation, such cells do not have significant immunoregulatory capacity. Under the proper circumstances, prosuppressor T cells may interact with a different set of activating T cells. This interaction could conceivably require direct surface membrane contact or could be mediated by soluble factors. It is likely that the prosuppressor T cells must divide in order to mediate suppression fully. Once the prosuppressor T-cell subset has differentiated into a suppressor effector T-cell subset, further cell division is probably unnecessary for suppressor activity.

The hypothesis developed from the use of the leukemic cells with prosuppressor T-cell properties provides at least two testable expectations for future clinical investigation. The first is that neoplastic diseases representing proliferations at different steps in suppressor-cell differentiation will be discovered. Exactly where the Japanese form of subacute T-cell leukemia with suppressor properties, described earlier in this paper, fits in cannot be answered at this time. Second, those patients with a neoplasm composed largely of suppressor effector cells will very likely have hypogammaglobulinemia directly related to their total tumor cell burden; however, those patients with a neoplasm of prosuppressor cells or suppressor activator cells will very likely have hypogammaglobulinemia related to the residual number or functional capacity of non-neoplastic cooperating T cells, as well as their leukemic cells. In such patients, it should not be surprising to learn that the serum immunoglobulin levels may not bear a direct relationship to the patient's neoplastic disease status and, indeed, may sometimes appear normal in spite of strong in vitro evidence for suppressor activity.

SIGNIFICANCE OF IMMUNOREGULATORY NEOPLASMS TO CLINICAL AND BASIC INVESTIGATION

The recognition that some T-cell leukemias or lymphomas may represent a homogeneous proliferation of T cells committed to either helper or suppressor function is important for a number of reasons. For example, certain forms of humoral immunodeficiency may be due to a helper-cell defect and not to intrinsically defective B cells alone or excessively activated suppressor cells. It is conceivable that neoplastic T-cell membrane-associated products or soluble factors released by neoplastic T cells could prove useful in the treatment of selected thymic-deficiency states. Such factors might be the starting point for synthesis of factors useful in thymic-deficiency states (or perhaps in those situations where it is desirable to augment a normal immune response, eg, as part of immunizations for overwhelming sepsis or even certain forms of cancer).

Neoplastic T cells may be the starting immunogens which could eventually make it possible to establish a reliable serologic marker system for immunoregulatory subsets in man. In mice, an extremely useful cell membrane marker system exists (16). This marker system is referred to as the Ly system of antigens, and depending on the Ly phenotype of the T cells, it is possible to quantitate and selectively eliminate helper and suppressor T-cell subsets in murine splenic subpopulations. Furthermore, in mice there is a crucial immunoregulatory subregion of the I portion of the major histocompatibility complex (H-2) (17). This chromosomal region is designated I-J, and genes clustered within this region may encode for suppressor cell function and certain suppressor factors. These I-J-encoded products may inhibit both cellular and humoral immune responses in a number of systems. Furthermore, antisera raised against I-J-encoded products may actually increase certain immune reactions. In fact, such antisera raised against I-J-gene products may even promote tumor rejection in certain mu-

rine systems, presumably by eliminating undesirable host suppressor cells that interfere with effective immune responses directed against tumor cells in vivo (18). The overall concept that suppressor cells may prevent the immune elimination of certain neoplasms is discussed in detail elsewhere (19).

The use of neoplastic human T cells with retained helper or suppressor function may speed the development of heterologous antisera which might be used to classify the immunoregulatory function of human T cells in analogy to the Ly and I-J systems of mice. Furthermore, we believe that it is now realistic to anticipate the development of antisera which can tilt the immunoregulatory balance in favor of helper or suppressor activity in vivo depending on the clinical requirements of patients with a variety of immunologically related disorders.

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Murine T-Cell Heterogeneity [1]

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SUMMARY

Immunoregulatory lymphoid cells that mature under the influence of the thymus gland (T cells) have been implicated to a major extent in the induction or at least the perpetuation of malignant neoplasms in man. Those T cells are thought to inactivate, suppress, or neutralize the normally occurring tumoricidal effector cells and thereby facilitate the unchecked growth of the neoplasm; the term "suppressor T cells" is therefore used to denote their individual activity. This concept implies that there is a balance between the effector cells and the suppressor cells in healthy subjects and that perhaps enrichment and activation of those cells involved in the defense against neoplastic growth, and specific depletion and elimination of those cells involved in suppression or inactivation of the former in patients with malignant diseases, may provide new modalities in cancer immunotherapy. Most of the studies that form the basis of this concept have been derived in animal models, particularly the mouse. The existence of cell-surface markers which have been used as phenotypic tools has provided the knowledge that distinct subpopulations of lymphoid cells do exist. The phenotypic characterization of lymphoid cells involved in functionally distinct immunologic events has been the object of intensive investigation. Therefore, the purpose of this paper is to briefly document our current knowledge of the functional heterogeneity that exists in murine T cells based on the differential expression of these cell-surface markers.

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Since many of these surface markers should be defined basically before beginning to establish their roles in differentiating subpopulations of murine T cells, several of them are briefly discussed in table 1. Use of anti-θ antisera (1) or anti-mouse thymocyte sera (ATS) in experimental protocols involving adult thymectomy and thoracic duct drainage showed that at least two populations of T cells could be defined on the basis of their ability to recirculate through the lymphoid system and their sensitivity to adult thymectomy (2). Those T cells which comprise the recirculating pool of lymphocytes were found to be relatively insensitive to adult thymectomy, but could be eliminated by administration of ATS in vivo. In contrast, a second population of T cells was identified which was relatively insensitive to in vivo ATS treatment and sensitive to adult thymectomy (3).

Studies of the maturation of T cells within the thymus indicate that a TL^-, θ^- precursor cell enters the thymic cortex and acquires both θ and TL antigens. At this stage, the cells are cortisone-sensitive; however, in what seems to be a further maturation, the cells move from the cortex to the medulla of the thymus and in the process lose the TL antigen and thus their sensitivity to cortisone (4). Thus, cortisone-resistant thymocytes are consid-

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TABLE 1.—Some important murine T-cell surface markers

Marker	Characteristics
θ	An alloantigen which is present on thymocytes, but not on their precursors. It seems that as maturation proceeds, the surface density of θ decreases. Although θ is the classic antigen used to identify T cells, it is also present on brain cells.
Thymocyte antigens	Tissue-specific antigens defined by heteroantisera prepared against mouse thymocytes or mouse brain and rendered specific for T cells by adsorption. Although distinct from θ, these antigens show the same time distribution and similar surface-density characteristics. The heteroantisera are generally considered equivalent to anti-θ serum in identifying T lymphocytes.
TL	A complex of 4 alloantigens which appear on cortical thymocytes and are lost as the cells enter the medulla. They are considered markers of very immature T cells.
Lyt 1, 2, 3	A system of 3 alloantigens which are apparently differentiation antigens of T cells. The majority of thymocytes are Lyt 1^+, 2^+, 3^+, but peripheral lymphocyte organs also contain Lyt 1^+, 2^-, 3^- and Lyt 1^-, 2^+, 3^+ cells, implying that Lyt 1^+, 2^+, 3^+ are precursors of Lyt 1^+ and Lyt 2^+, 3^+. Lyt 2 and Lyt 3 are genetically linked to each other, but not to Lyt 1.
Ia	Alloantigens coded for by genes located in the I region of the mouse MHC. Although present to a much larger extent on the non-T bursa-derived or B lymphocytes, they also seem to be present on a small fraction of resting and activated T lymphocytes.
Fc receptor	A receptor for the Fc portion of Ig. Receptor binds aggregated Ig and Ab-Ag complexes. Complement is not required for binding. It is present on B lymphocytes, macrophages, and some, but not all, T lymphocytes.
Recognition structure (idiotype)	The specific antigen receptor of T cells corresponds to, but is not identical with, surface Ig of B cells. It can be detected either by binding of specific antigen or antirecognition structure (idiotype) antibody. At the finest degree of resolution, this is a clonal marker of T cells.

ered to be a more mature T-cell population and have the properties of immunocompetent peripheral T cells (5).

The first evidence that the T-cell pool was functionally heterogenous was provided by Cantor and Asofsky (6) through their investigation of lymphocyte synergy in the graft-versus-host (GVH) reaction. They found that two populations of T cells when mixed together in an appropriate ratio gave a much larger GVH reaction than the sum of each population considered separately. The cells were designated as T_1 and T_2 and were found to have the following characteristics: T_1—found predominantly in the thymus and spleen and relatively sensitive to adult thymectomy. They are the actual effector cells in the GVH reaction. T_2—found in lymph nodes, peripheral blood, and spleen and relatively sensitive to in vivo ATS treatment. These T cells are considered amplifiers of the GVH activity of the T_1 cells.

From their properties, it is clear that the T_1 cells closely resemble the noncirculating, less mature T cell, sensitive to cortisone and adult thymectomy; the T_2 cells are similar to the recirculating cells characterized by sensitivity to ATS in vivo. Further studies by Cantor (7) showed additional similarities between T_1 and immature T cells and T_2 and the more mature population. By titrating the sensitivity of T_1 and T_2 cells to anti-θ + complement treatment, it was found that T_1 cells were sensitive to higher dilutions of the antisera, presumably reflecting a higher cell-surface density of θ antigen. Since it had previously been shown that T cells lose cell-surface θ in the process of maturation, this was taken as further evidence that T_1 cells represent less mature T cells than T_2.

Until now, although heterogeneity among T cells has been defined functionally, rapid advances in the field of immunogenetics and the availability of various inbred and congenic strains of mice paved the way for the discovery of cell-membrane alloantigen determinants (CMAD). Thus, to date there have been at least 40 different loci which have been

shown to code for these CMAD (8). The existing findings with CMAD led to the observations that these antigens could be used to distinguish between different functional subpopulations of not only the T-cell lineage but also the B-cell lineage, leading to the classification of these subsets both in terms of function and the cell-surface phenotype. This classification has proven to be of immense importance in studies of the maturation and differentiation of lymphoid cells and the examination of lymphoid tumors and normal lymphocyte function. While several CMAD have been shown to be present on T cells, this paper will focus its attention on anti-Lyt 1, 2, and 3, which have been used quite extensively by several laboratories, and form the backbone of the existing literature on T-cell subclasses.

The Ly antigens were originally detected as contaminating specificities present in antiserum used for typing murine leukemias. Further characterization determined that two alleles of each antigen exist and that the antigens are present only on lymphoid T cells (θ^+) and therefore are termed Lyt antigens (9). However, the demonstration by Cantor and Boyse (10) that these are in fact differentiation antigens of T cells, which can be used to separate functional T-cell subpopulations, has led to the definition of at least three major subclasses of T lymphocytes: those that bear all three Lyt alloantigens, 1, 2, and 3 (1^+, 2^+, 3^+); those that predominantly bear Lyt 1 (1^+, 2^-, 3^-); and those that predominantly bear Lyt 2 and 3 (Lyt 1^-, 2^+, 3^+).

The majority (> 80%) of murine thymocytes and of neonatal peripheral T cells are Lyt 1^+, 2^+, 3^+, suggesting that this phenotype defines a very immature T cell. As the animal matures, the pool of peripheral T cells changes to 30% Lyt 1^+, 2^-, 3^- and 8% Lyt 1^-, 2^+, 3^+. In addition, it has been found that Ly 1^+, 2^+, 3^+ lymphocytes are resistant to adult thymectomy and cortisone treatment, whereas the fraction of cortisone-resistant thymocytes which are Lyt 1^+, 2^+, 3^+ is only 20% (10). These results suggest that immature T cells acquire all three Lyt antigens in the thymus, and as they mature and enter the peripheral pool, a percentage of these become Ly 1^+ or Ly 2^+, 3^+. This further suggests that Lyt 1^+, 2^+, 3^+ cells in the peripheral lymphoid tissues represent the T_1 cell originally described by Cantor and Asofsky. At present, two possible models exist for the description of the sequence of Ly phenotype maturation (11). The first model predicts that the three subclasses of T cells arise from three distinct precursor cells, and the second model predicts that Ly 1^+, 2^-, 3^- and Ly 1^-, 2^+, 3^+ cells are the progeny of a primitive Ly 1^+, 2^+, 3^+ T-lymphocyte pool. However, evidence from ontogeny experiments supports the second model.

The early studies of Cantor and Boyse (11) showed that Lyt antisera could define two T-cell populations acting synergistically in the generation of cytotoxic lymphocytes for allogeneic targets. Since that initial discovery, a number of functions have been described for cells bearing a given Lyt phenotype; however, we hasten to add that possession of a similar Lyt phenotype by functionally distinct cells does not imply that such cells are related in any way except by their Lyt phenotype. A general review of the functions ascribed to three major classes of T cells, based on the Lyt phenotype, follows. (In this regard, it is important to point out that the functional characterizations are based on the cytotoxic potential of the anti-Lyt sera in the presence of complement. The reason for this note of caution is the recent evidence by Mathieson et al that it is not the absolute absence of Ly 1 or Ly 2, 3 on the surface of the cell, but a difference in the relative density of each of these markers that makes it susceptible or refractory to the cytotoxic potential of a given antisera. These data were derived using the Fluorescence Activated Cell Sorter.)

Lyt 1^+, 2^-, 3^- Cells

The Lyt 1^+, 2^-, 3^- population was first shown by Kisielow et al (12) to provide T-cell help in the in vitro response to sheep red blood cells. Although this experiment involved antigen-primed T cells, the results have been confirmed for primary immune responses in vitro (11). Thus, Lyt 1^+ cells or their products are apparently an obligatory component of humoral immune responses to thymus-dependent antigens (11). Classically, helper T cells have been characterized as antigen-specific, nylon-wool nonadherent, and Ia^-; however, recent studies by Tada et al (13) of T cells primed to antigen in vivo have shown that in addition to such Lyt 1^+, 2^-, 3^- classic helper T cells, there exists in the primed population a nylon-wool adherent Ia^+, Lyt 1^+, 2^-, 3^- cell which, once re-stimulated by specific antigen, provides nonspecific help for humoral immune responses. In addition to the obligatory role Lyt 1^+, 2^-, 3^- cells play in humoral responses, the early studies of Cantor and Boyse (11) showed that cells of this phenotype could amplify cytotoxic responses to allogeneic target cells. It was further demonstrated that the Lyt 1^+, 2^-, 3^- cell responded to the antigen coded by the I region of the major H-2 histocompatibility complex (MHC), while the cytotoxic response was directed against K or D region-coded antigens of the MHC (14).

Previously, Lyt 1^+, 2^-, 3^- cells did not appear to perform any effector functions other than to direct

the maturation of other cells, such as B cells, in humoral responses; however, it was recently reported that Lyt 1^+, 2^-, 3^- cells from sheep red blood cell-primed mice could initiate a delayed-type response when transferred into T cell-depleted mice and challenged with antigen (15). At present, it is not clear whether these cells are actually the effectors in this case or serve to recruit other cell types which mediate the response.

Ly 1^-, 2^+, 3^+ Cells

Whereas Lyt 1^+, 2^-, 3^- lymphocytes are ascribed the majority of helper-cell functions, it has become increasingly clear that Ly 1^-, 2^+, 3^+ lymphocytes are responsible for a large number of cytotoxic and suppressor activities (11). Both functions are probably not mediated by the same cell, since cytotoxic cells are considered Ia^- and Lyt 1^-, 2^+, 3^+, while suppressor cells are Ia^+ (16). Thus far, Lyt 1^-, 2^+, 3^+ cytotoxic cells have been described for allogeneic targets (primarily directed against K or D region-coded antigens) and for chemically modified syngeneic targets (11). The precursors of these cytotoxic cells are also Lyt 1^-, 2^+, 3^+ and require interaction with other Lyt subpopulations for their functional maturation.

Ly 1^+, 2^+, 3^+ Cells

Although the Lyt 1^+, 2^+, 3^+ cells were originally thought to exist largely as precursors for Ly 1^+, 2^-, 3^- helper cells and Ly 1^-, 2^+, 3^+ suppressor cells (as shown by Feldmann et al [16] [fig 1]), it is now clear that these cells also have functional properties, particularly in the area of immunoregulation. Suppressor cells bearing the Lyt 1^+, 2^+, 3^+ phenotype have been identified in GVH reactions (17), neonatal thymus (18), and adult spleen (11). One important characteristic of these suppressor cells is that they apparently do not require previous contact with antigen; that is, no apparent maturation is necessary. Recently, Bach and Alter (14) found Lyt 1^+, 2^+, 3^+ cells to participate in the generation of cytotoxic T cells to targets differing from the effector population at only the K or D region of the H-2 complex. The role of Lyt 1^+, 2^+, 3^+ cells in such responses is further emphasized by the experiments of Shiku et al (19) who compared phenotypes of cytotoxic cells directed at either allogeneic or syngeneic tumor cells. It was noted that the cells cytotoxic for an allogeneic tumor were Lyt 1^-, 2^+, 3^+, while those cytotoxic for a syngeneic tumor were Lyt 1^+, 2^+, 3^+. This finding is similar to that of Bach and Alter (14), since the syngeneic tumor would lack I-region differences with the responder. It has been suggested that Lyt 1^+, 2^+, 3^+ cells serve as a homeostatic or feedback control mechanism to maintain balance within the immune system (20,21). This theory derives some support from the fact that New Zealand black mice develop autoimmune disease concomitant with a loss of Lyt 1^+, 2^+, 3^+ cells and a loss of suppressor function. These results, in addition to providing evidence of effector activity for Ly 1^+, 2^+, 3^+ cells, also suggest the existence of a subpopulation within the Ly 1^+, 2^+, 3^+ phenotype group, and thus, further support the single precursor model for Lyt maturation.

A summary of the current knowledge of T-cell interactions is shown in figure 1. The complexity portrayed in the figure is due largely to the numerous interactions T cells participate in, forming a system of checks and balances. As drawn here, the system seems unidirectional, with the life style of each cell being decided before exit from the thymus. Experiments supporting this point of view have shown that thymectomized, X-irradiated mice repopulated with anti-Ly + complement-treated spleen cells retain only those T-cell functions associated with the Ly phenotype of the T cells used for reconstitution (22). Thus, it is clear that Lyt 1^+, 2^-, 3^- and Lyt 1^-, 2^+, 3^+ are precommitted in such a manner as to rule out transition from one functional phenotype to the other. Whether such precommitment is characteristic of Lyt 1^+, 2^+, 3^+ cells is yet to be determined.

Another level at which T-cell heterogeneity can be studied is the one which dictates the antigenic specificity of the various T-cell clones. In molecular terms this is conferred by the antigen receptor or recognition structure, whose counterpart on the B cells is the immunoglobulin molecule. In contrast to the functional manipulation possible with anti-Lyt sera, antisera specific for a given recognition structure would permit antigen-specific manipulation of the T-cell population. Very recently, such studies have found that antigen-specific reagents directed against the recognition structure, which seemingly recognize idiotypic determinants, can in certain experimental systems be used to selectively stimulate or abrogate specific immune responses (23). The possible therapeutic implications of the use of these anti-idiotype sera are enormous and their development and clinical testing will provide a novel approach for immune-therapeutic strategies.

The studies of T-cell heterogeneity were originally stimulated by our desire to understand the role of the immune system in protecting the organism from internal and external threats. At our present level of knowledge, it appears that selective manipulation of immune responses for the betterment of the organism's health is an attainable goal. Thus, con-

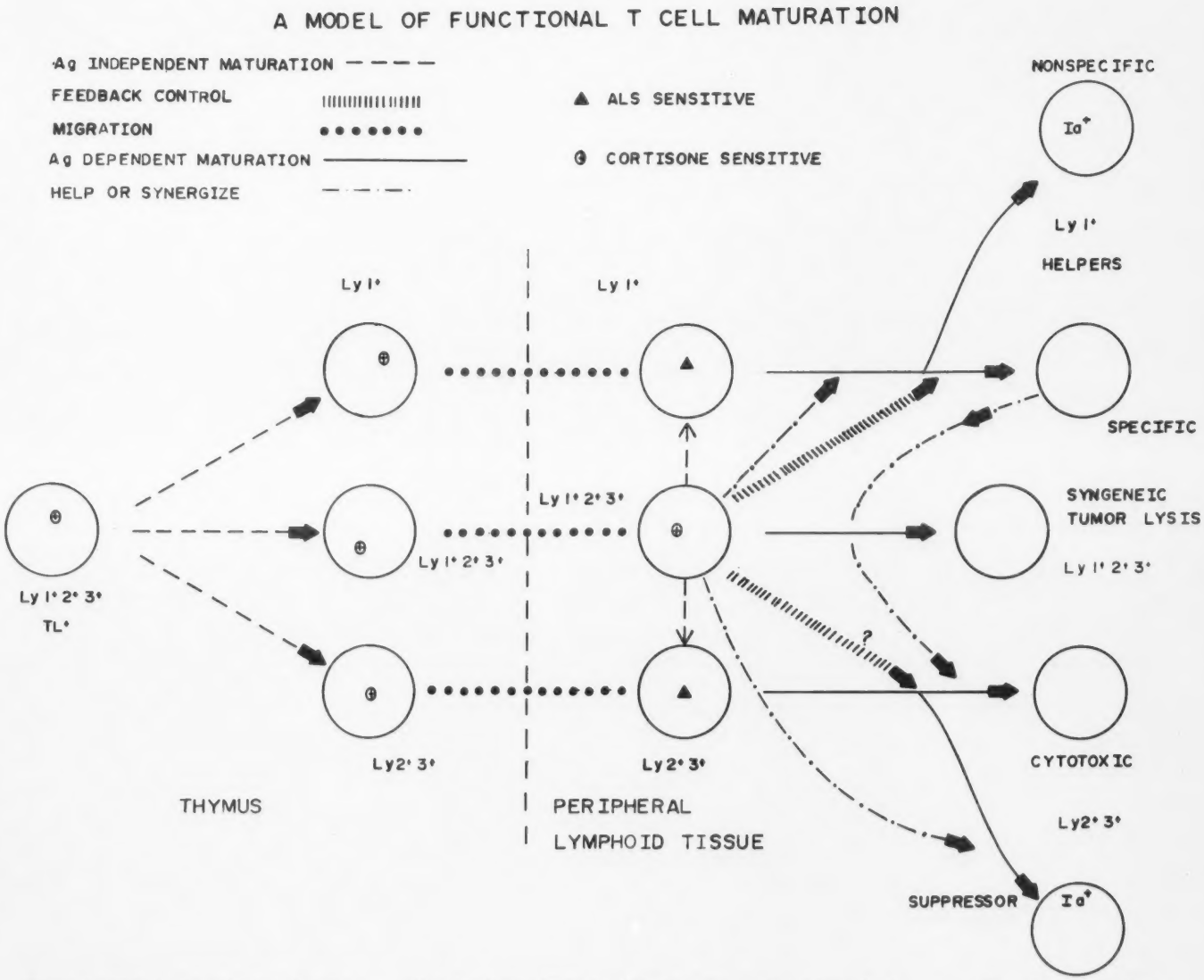

FIGURE 1.—This simple model, based on the assumption that the Ly 1+, 2+, 3+ cell is the precursor for all Ly+ cells, is a compendium of the interactions of Ly+ cells and their effector capabilities, as shown in the text.

tinued effort in this area is easily justified on the basis of immunotherapy.

The presence of certain T-cell markers but not other markers on certain lymphocytic leukemia cells suggests that the neoplasm is a restricted proliferation of a particular T-cell lineage or subclass. The identification of the repertoire of T-cell surface markers on a particular neoplasm thus not only provides a clue to the T-cell subclass of neoplasm, but also suggests a particular functional immunologic dysfunction or impairment. On the other hand, certain neoplasms retain their original functional property and this indeed has been true for those patients with a leukemia or lymphoma of T-cell origin who manifest a hypogammaglobulinemia (24).

Therefore, these data permit the use of phenotypic markers as tools for the diagnosis of a particular type of leukemia or lymphoma and, with the knowledge of the function of the particular phenotype-bearing cell, various immunomanipulative forms of therapy can be envisioned for the treatment of neoplasia.

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Preliminary Evaluation of 15 Chemotherapeutic Agents Applied Topically in the Treatment of Mycosis Fungoides

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SUMMARY

This is an interim report of a double-blind multi-institutional study to examine the effect of chemotherapeutic agents applied topically to patients with mycosis fungoides. To date, 41 patch tests have been completed using 15 drugs. Five of the drugs produced some improvement, four were highly irritating, and six had no effect. This patch-testing study is a prelude to more extensive therapy trials.

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Some patients treated with topical mechlorethamine during the early cutaneous stage of mycosis fungoides (MF) achieve remission (1). Furthermore, BCNU has been found to be effective when used topically in some patients with MF (2). Several chemotherapeutic agents have an inhibitory effect when used topically in psoriasis (3,4), a condition often likened to a malignancy in terms of rapid cell turnover. It therefore seems likely that additional chemotherapeutic agents may be effective when applied topically. Topical screening may also prove to be an effective method for selecting agents active systemically in MF.

PROTOCOL

Patients with early eczematous and plaque-stage MF were referred to this study from the Mycosis Fungoides Cooperative Group (5), which presently follows > 450 patients with varying stages of disease, and the American Society of Dermatopathology, whose members notify the cooperative group when they make a diagnosis of MF.

STUDY DESIGN

Twenty-four chemotherapeutic agents (table 1) are being tested at ten collaborating institutions throughout the US. Each drug is tested at four sites using three concentrations (1×, 5×, and 0.2×) and a vehicle control. The amount of drug used at the 1× concentration is based on the formulas shown in figure 1 which assume: (*a*) that the drug is completely absorbed; and (*b*) that the amount of drug applied to the whole body topically would be no more than the usual amount given systemically over the same 3-week trial period. However, the few experiences documented in the literature (6,7) as well as initial trials on our part suggested that increasing the topical dose by a factor of 4 was necessary to bring the 1× concentration into a therapeutic range. This increase was incorporated into the formula.

Drugs are applied to the 1.7 × 1.7-cm² gauze area of a 3.0 × 3.0-cm² patch three times a week for 3 weeks and each application is left in place for 12 hours. A shorter overall time period was tried in which patches were applied for 12 hours each day for 9 consecutive days; however, that technique did not produce as great a response as the longer 3-week trial. Test sites are randomly selected so that

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Equation 1

$$\frac{\left(\begin{array}{l}\text{total mg of drug}\\ \text{administered in}\\ \text{usual 3-wk systemic-}\\ \text{therapy regimen}\end{array}\right)\left(\begin{array}{l}\text{area of patch =}\\ \frac{2.89\ \text{cm}^2}{\text{area of standard}}\\ \text{man = 20,000 cm}^2\end{array}\right)}{\left(\begin{array}{l}\text{No. of treatments for}\\ \text{planned 3-wk therapy}\\ \text{regimen = 9}\end{array}\right)\left(\begin{array}{l}\text{6.2 = 1x + 5x + 0.2x}\\ \text{where x = standard}\\ \text{topical solution}\end{array}\right)} \times \frac{1\ \text{g}}{1000\ \text{mg}} \times 100 \text{ (to read as \%)}$$

volume needed to cover 2.89 cm^2 = 0.0087 mg if 60 ml needed for standard man surface area

(conversion of mg to g)

X4* = % standard topical solution

5 (% standard topical solution) = 5x solution

2 (% standard topical solution) = 0.2x solution

Equation 2

$$\%\ \text{standard topical solution} \quad \frac{\text{g}}{100\ \text{ml}} \times \frac{1000\ \text{mg}}{\text{g}} \times \text{9 treatments (0.15 ml) (volume applied into each tape patch)} = \text{No. of mg of standard topical solution used in planned 3-wk therapy regimen}$$

5 (No. of mg for standard topical solution) = No. of mg of 5x topical solution used in planned 3-wk therapy regimen

0.2 (No. of mg for standard topical solution) = No. of mg of 0.2x topical solution used in planned 3-wk therapy regimen

*Factor to allow for ratio of planned topical amount of drug to usual systemic therapy amount to equal 1%

FIGURE 1.—Formulas used to determine dose of drug.

TABLE 1.—Comparison of topical vs systemic doses of patch-test drugs

Drug	Total drug (mg/standard adult male) administered in usual 3-wk systemic-therapy regimen	Total drug (mg/total course) administered in planned 3-wk topical-therapy regimen	Topical/systemic (%)
Actinomycin D	2.5	0.025	1.0
Adriamycin	150	1.512	1.0
Cytosine arabinoside	4480	44.9	1.0
β-2'-Deoxythioguanosine	21	0.211	1.0
DTIC	2500	25.04	1.0
Emetine	546	5.46	1.0
5-Fluorouracil	4800	83.7	1.7
Guanazole	52,500	262.1	0.50
Hydroxyurea	44,000	217.6	0.50
Melphalan	122	1.25	1.0
6-Mercaptopurine	3675	36.8	1.0
Methotrexate	150	3.0	2.0
Methyl-CCNU	450	37.68	8.4
Methyl-GAG	1680	16.8	1.0
Procarbazine	4200	42.04	1.0
6-Thioguanine	2940	29.40	1.0
ThioTEPA	200	2.008	1.0
Vinblastine	21	0.211	1.0
Vincristine	8.4	0.0842	1.0
VM-26	300	3.0	1.0
Azaserine	14,000	35.15	0.25
5-Bromodeoxyuridine	250	2.43	1.0
Dianhydrogalactitol	420	4.2	1.0
Dichloromethotrexate	1750	17.49	1.0

TABLE 2.—Patch-test results (41 tests)

Agent	3-wk patch-test results*		
	Improvement	Irritation	No change
Cytosine arabinoside	××	×	
Dianhydrogalactitol	××		
DTIC	×		×
Guanazole	×		×
VM-26	×		
5-Fluorouracil		××××	
Hydroxyurea	×	×	××
6-Thioguanine		×	×
ThioTEPA	×	××××	
Actinomycin D			×
6-Mercaptopurine			××
Methotrexate	×		××××
Methyl-GAG			××××
Procarbazine			×××
Vincristine			×

*Each × = 1 patient.

dilutions of the same drug are not adjacent to each other. The outer limits of the patch are marked in indelible ink and the area is photographed prior to the first application. Photographs are also taken of any site when it is considered to have been altered by the test agent. Laboratory tests including cbc, SGPT, SGOT, alkaline phosphatase, uric acid, and urinalysis are done initially and repeated as indicated by the protocol.

RESULTS

The amount of agent used topically during the 3-week period of testing is usually ≤ 1% of the total amount used systemically for the treatment of other malignant diseases during the same 3-week period (table 1). To date, no systemic toxicity has been experienced with these drugs. Patch tests have been completed for 15 of the 24 test drugs as of this report. The results are shown in table 2.

Table 2 summarizes patch-test results in three categories: improvement, irritation, and no effects. Five drugs have shown some improvement, four have been predominantly irritating, and six have shown no effect. New referrals for this protocol are welcome.

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Treatment of Mycosis Fungoides With Topical BCNU

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In 1975 we reported favorable results with topical applications of several nitrosourea compounds in 26 patients with mycosis fungoides (MF) (1). To date, 40 patients with MF or related conditions have been treated topically with BCNU and, with the exception of early treatment failures, they have been followed for at least 6 months. Schedules for total-body treatment have usually consisted of 14–21 daily applications of 40–60 mg of BCNU in dilute alcohol for a total of 560–1260 mg. More recently, alternate-day schedules of 25–50 mg × 8 for a total of 200–400 mg have been used. Small numbers of lesions are also treated locally with 0.2% BCNU in 95% alcohol or 0.4% BCNU in white petrolatum one or two times per day.

Results are presented in table 1. Satisfactory control means that either (*a*) after initial complete remission recurrent lesions are readily cleared with repeated total-body or local treatment or (*b*) after initial clearing the patient has remained clear at this writing for at least 6 months without further treatment; seven patients were in this latter category.

Some degree of dermatitis, including simple erythema, was seen in all patients and was severe in 13 (33%). Contact hypersensitivity occurred in four (10%) patients. Posttreatment telangiectasia affected 14 (35%) patients and persisted for > 1 year in five. Hyperpigmentation lasting for > 1 year occurred in an 84-year-old man.

Mild bone marrow depression occurred in nine of 30 patients treated with total-body courses of BCNU. The leukocyte count fell to < 3500/mm^3 and the platelet count to < 100,000/mm^3 in three other patients. With the exception of a temporary BUN elevation in one patient there were no other changes in SMA–12 blood chemistry panels associated with treatment. No deaths resulted from treatment. Three patients have received total doses of BCNU ranging from 4.2 to 5.4 g applied intermittently over a period of 42–61 months without experiencing apparent harmful effects.

TABLE 1.—Response of MF and related conditions to topical BCNU

	No. of patients	Satisfactory control*	Median mos of followup (range)
Universal poikiloderma	1	0	4 (4)
Parapsoriasis en plaques	2	2	25 (13–26)
MF stage†			
1	3	3	9 (6–20)
2	21	16	22 (6–60)
3	9‡	5	24 (6–61)
Sézary syndrome	4	0	1 (1–6)

**See* text for explanation.

†Stage 1 = minimally infiltrated plaques; stage 2 = moderately infiltrated plaques; and stage 3 = deeply infiltrated plaques, tumors, or ulcers.

‡Treatment limited to early recurrences after electron-beam therapy.

BCNU does not cross-react with mechlorethamine and therefore can be used in patients allergic to the latter drug. Most patients can treat themselves at home. BCNU is stable for at least 3 months in 95% alcohol in the refrigerator (4°C–5°C) (2), and the ointment appears stable indefinitely at room temperature.

Recent results with the alternate-day schedule using total doses of 200–400 mg are favorable. This suggests that satisfactory control may be achieved with a lessened hazard of cutaneous reactions and bone marrow depression.

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Radiation Therapy in the Management of Cutaneous T-Cell Lymphomas [1]

Richard T. Hoppe, [2,*] Zvi Fuks, [3] and Malcolm A. Bagshaw [2,4]

SUMMARY

The lesions of mycosis fungoides (MF), a neoplasm of T lymphocytes, are extremely radiosensitive. The history of ionizing radiation in the treatment of MF is discussed in this paper. Low-energy X-rays have long been successful in the treatment of individual lesions and in the effective palliation of patients with this disease. The major breakthrough in the treatment of MF with ionizing radiation came with the development of the ability to treat the total skin by means of electrons which penetrate to depths of only 1–2 cm, thereby treating the epidermis and dermis while sparing more deeply situated tissues. The complications and results of this therapy are reviewed. The aggressive use of electron-beam therapy has resulted in many long-term remissions. It is important to use high initial doses of radiation and to treat patients when they are still in the early stages of disease. The potential use of other modalities of radiation, including total-lymphoid radiation with megavoltage photons, low-dose fractionated total-body radiation, and sequential hemibody radiation, are reviewed.

[Cancer Treat Rep 63:625–632, 1979]

Ionizing radiation has been used in the treatment of mycosis fungoides (MF) since 1902, when Scholtz (1) first reported on the treatment of MF lesions with the recently discovered "roentgen-rays." For several decades the only X-rays available were of low energy and superficial penetration, and the cutaneous lesions of MF were therefore considered an excellent model for evaluating the therapeutic potential of the new beams. The striking radiation sensitivity of MF lesions impressed the early radiation therapists. We now know that the malignant cells of MF and Sézary's syndrome, neoplastic thymus-derived lymphocytes, are among the most radiosensitive of all cells. This sensitivity is shared by the normal T and B lymphocytes of the lymphoid tissue and peripheral blood as well as by the neoplastic lymphocytes of many of the other malignant lymphomas. Normal human peripheral blood lymphocytes undergo an interphase death within a few hours after radiation exposure (2). Radiation-induced damage is detectable in vitro after exposures as low as 2–5 rads (3). Clinically, peripheral blood lymphocytopenia is observed early during the course of therapy in patients undergoing a fractionated course of radiation for treatment of malignancy (4). Fractionated total-body radiation delivered at a rate of 30–50 rads/week, as in the treatment of advanced-stage nodular lymphomas, produces severe lymphopenia after cumulative doses of only 100–150 rads (5).

Because of the radiosensitivity of MF lesions, radiation has long been established as one of the most effective therapies for this disease. As the techniques of radiation have developed over the years, so has their application to the treatment of MF and other T-cell lymphomas. Some of these developments will be reviewed in this paper.

Orthovoltage X-Rays

The early approach to the treatment of MF was entirely palliative. Individual lesions were treated

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with low doses of soft X-rays (60–100 kv; half-value layer, 1–1.5 mm Al) given at a rate of 75–100 rads weekly with total doses of 600–800 rads (6). Although disease within a treated area was often controlled for a long period of time, over subsequent years patients inevitably returned on many occasions for treatment of new cutaneous lesions (7). Most patients eventually died from sepsis due to progression of cutaneous disease or from extracutaneous spread of lymphoma. This led to the impression that MF was incurable, although in many cases it might progress slowly over the course of many years. It was felt, therefore, that the treatment should be palliative, with minimal therapy deferred, whenever possible, until the disease was in its late and final stages (8).

Small-field ("spot") orthovoltage radiotherapy is still being used successfully in the treatment of plaques and tumors in patients with recurrent disease who do not respond to other forms of treatment. Moderate-size fractions (300–500 rads) and relatively low total doses (800–1500 rads) are usually adequate to achieve permanent control of such lesions.

In view of the good local control which could be achieved with orthovoltage radiation in MF, it is not surprising that attempts were made to treat large fields with high doses in order to achieve a more complete response. Such extensive high-dose treatments were not well-tolerated and were frequently ineffective due to extension of disease outside the treatment fields. In 1939, Sommerville (9) suggested a method of total-skin "X-ray-bath" radiation at a rate of 10 rads/day to a total dose of 200–900 rads. Although highly effective, the complications were severe and ranged from acute radiation dermatitis to agranulocytosis and death. These complications have discouraged the use of total-body superficial X-ray therapy for the treatment of MF. Recently, Le Bourgeois et al (10) have described a technique for total cutaneous superficial radiation by means of a fixed 55-kv X-ray generator and a moving couch. This complicated treatment technique enables the delivery of relatively high radiation doses distributed homogeneously in the skin, with low penetration to deep tissues. The short-term results of the use of this technique in MF have been excellent and the acute and chronic complications in the first 25 patients are reported to be minimal.

Electron-Beam Therapy

The impressive remissions observed in some patients treated with the total-skin "X-ray-bath" technique stimulated the pioneer work of Trump et al (11) in the use of 2.5-mev electrons for total-skin radiation. Electrons have a limited range of penetration and deposit their total energy within this range. The radiobiologic effect of electrons is therefore limited to superficial tissues, with the radiation dose distribution and maximal depth of penetration dependent upon their energy. This provides a means for radiating the entire body surface area, while sparing the deeper tissues.

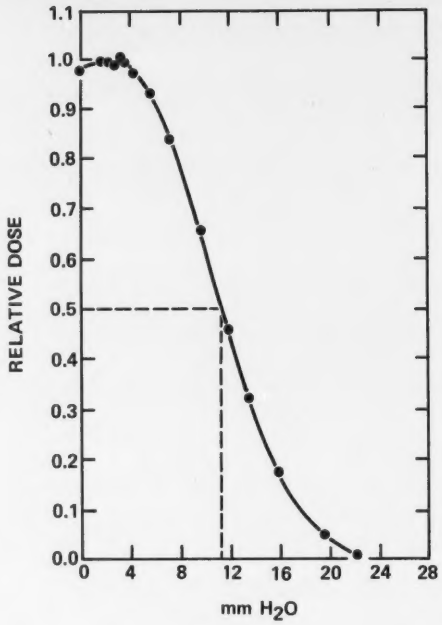

FIGURE 1.—Relative depth dose distribution in the treatment plane for a single ± 20° dual-exposure field. The extrapolated range of the curve suggests 4.0 mev for the energy of the electrons at the surface of the patient. (Figure provided courtesy of Peter Fessenden, PhD.)

Electron-beam energies ranging from 2.5 to 7.0 mev have been suggested for the treatment of MF (11–15). Figure 1 shows, as an example, the depth dose distribution of the 4-mev electron beam currently used for the treatment of MF at Stanford University. Maximum ionization occurs within the first 4 mm beneath the skin surface with a rapid fall-off of dose thereafter. The 50% depth dose is at 11.4 mm and the dose at 20 mm is < 5% of the maximum. Since the infiltrates of MF involve primarily the epidermis and dermis, this beam is adequate for the treatment of most lesions. The limited penetration of the electrons is advantageous in that it spares the mucous membranes, bone marrow, gastrointestinal tract, and other vital or-

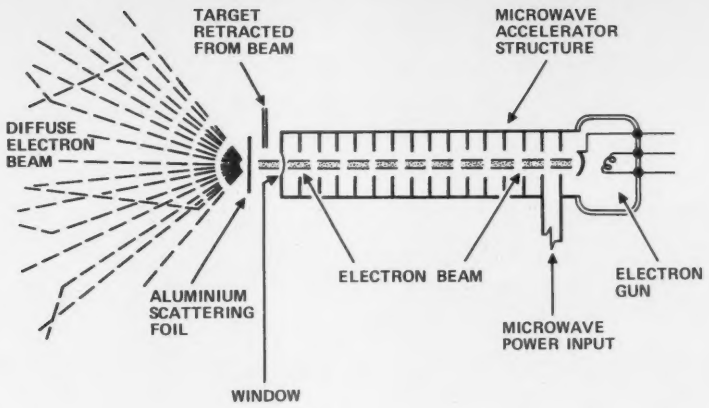

FIGURE 2.—Arrangement for production of scattered electron beams by a linear accelerator.

gans which would commonly be affected by X-ray radiation.

Treatment techniques have varied according to the equipment and facilities available at each institution (11–15). Since 1972, patients have been treated at Stanford University with a 4-mev beam produced by a Clinac-10 (Varian) linear accelerator utilizing the stationary dual-exposure technique (14). The patient stands at a distance of 10 feet from the accelerator. The beam is spread over the entire skin surface by having it pass through an aluminum scattering foil (fig 2). A horizontally directed beam does not provide adequate dose uniformity in the vertical plane of the patient, so the beam is angled alternately 20° above and below the horizontal providing a homogeneous dose distribution over an area of approximately 7 × 4 feet (figs 3 and 4). In addition, by this technique, the central axis of the electron beam, which contains most of the beam's photon contamination, passes above or below the patient. In fact, the measured percentage of X-ray contamination in the treatment plane for a single dual-field exposure does not exceed 0.3%.

Patients at our institution are treated in the

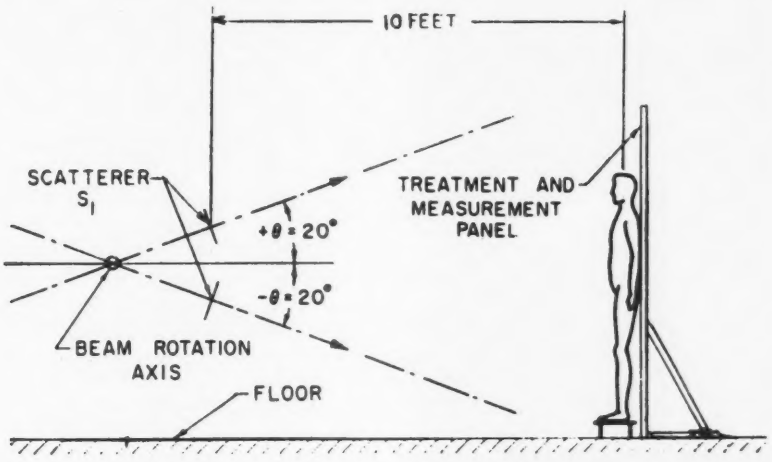

FIGURE 3.—Patient stands 10 ft from the linear accelerator. Angling of the beam alternated 20° above and below the horizontal ensures that the central axis does not pass through the patient and guarantees minimum photon contamination of the beam.

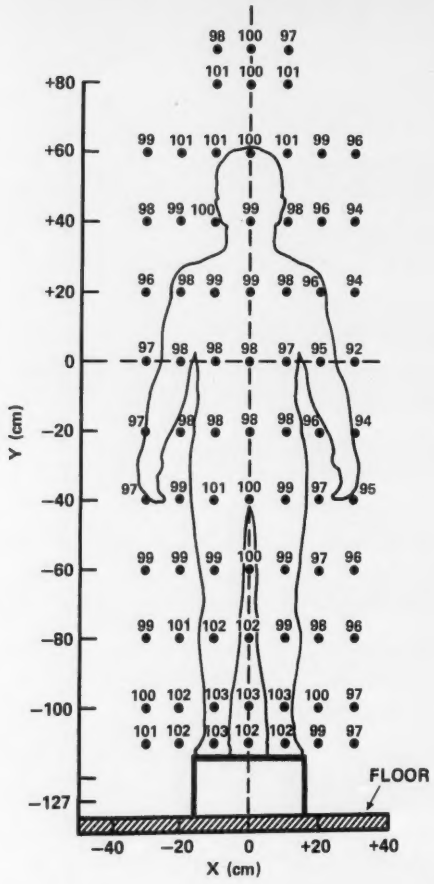

FIGURE 4.—Dose distribution in the treatment plane from a single ± 20° dual-exposure field of the electron beam normalized to 100 at the center of the treatment plane. (Figure provided courtesy of Peter Fessenden, PhD.)

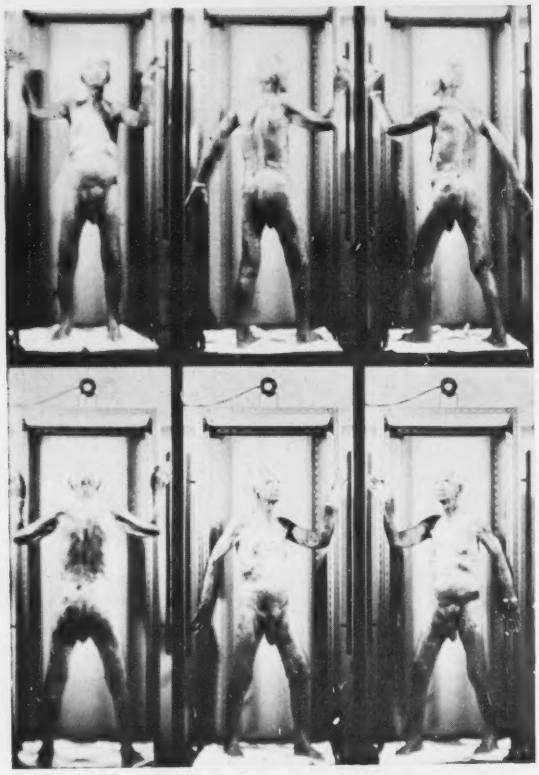

FIGURE 5.—Patient in treatment positions for the 6-field treatment technique.

standing position by a multiple overlapping-field technique. The orientation of the patient with respect to the beam axis and the positioning of the extremities are different for each field. The original technique used four body positions—anterior, posterior, and opposed laterals—but since 1968, this has been replaced by a six-field technique (fig 5) to ensure a more homogeneous distribution of radiation to the skin (14).

In the six-field technique patients are treated using anterior, posterior, and four oblique fields arranged in 60° increments about the vertical axis during each treatment cycle. Each field consists of two equal components, one with the central axis of the beam aimed 20° above the horizontal and the other pointing 20° below, with the combination referred to as a ± 20° dual field. A complete six-field treatment cycle requires 2 consecutive treatment days. On the first treatment day the anterior and the two posterior oblique fields are treated and on the second day the posterior and the two anterior oblique fields are treated (fig 6). Two such treatment cycles are completed per week.

The overall skin dose for a six dual-field treatment cycle is calculated as a product of the dose delivered to the center of the treatment field for one of the dual fields multiplied by a correction factor (F) (14) (fig 6). Factor F accounts for the fact that there is an overlap of the various dual treatment fields and that any point on the surface receives radiation from more than one of the fields. It is calculated from phantom measurements performed during a treatment sequence in which all dual exposure fields are used to cover the entire circumference of the phantom. The tolerance of individual patients to the electron beam is variable, but doses

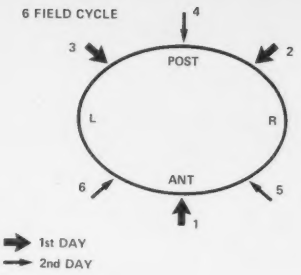

FIGURE 6.—Current treatment technique with the 6 ± 20° dual-exposure fields. The average skin dose for a 6 dual field cycle is the product of that dose delivered to the center of the treatment plane for a single ± 20° dual-exposure field and a multiplication factor (F). Factor F is calculated from phantom measurements performed during a treatment sequence in which all 6 dual-exposure fields were employed.

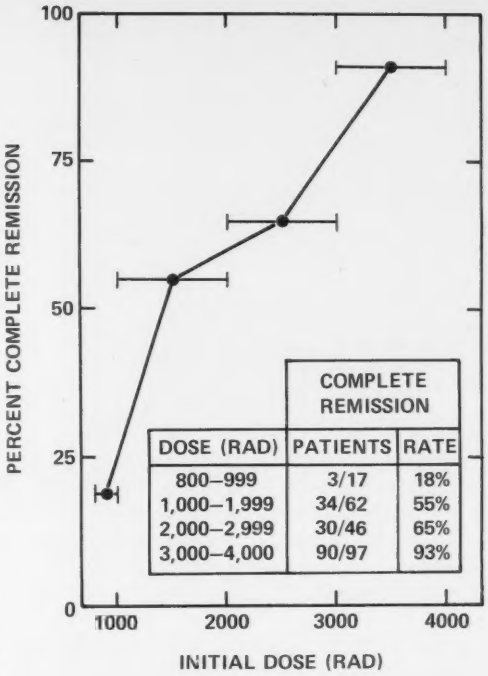

FIGURE 7.—% complete regression of all cutaneous lesions following the first course of electron-beam therapy as a function of total dose. The data are compiled for all stages of disease. Horizontal bars and brackets = dose ranges.

of 200 rads/cycle and total doses of 3000–3600 rads in 8–9 weeks are well-tolerated by most.

Because of the minimal penetration of the electrons, only those portions of the skin which are directly exposed to the beam are radiated. The normal variations in the shape, orientation, and contour of the body and the presence of intertriginous areas require special positioning of the patient or supplementary boosts to obtain dose uniformity over the entire skin surface. Areas not directly exposed to the electrons such as the soles and the perineum need to be treated with separate electron-beam fields or with orthovoltage radiation (120–200 kv). When involved with MF, the skin over the top of the skull also requires such specially designed radiation fields.

The only organ routinely shielded from the electron beam is the eyes. When the eyelids are involved, specially prepared contact lenses made of lead (5-mm thick) are interposed between the lid and the cornea within the conjunctival sac. Otherwise, external 5-mm lead eye shields are taped to the eyelids to protect the cornea and lens from the effects of radiation. Also, when disease is not present distal to the elbows or knees, nail shields are provided to prevent anonychosis.

This treatment is well-tolerated by most patients, with minimal acute morbidity or chronic complications. An exacerbation of cutaneous lesions frequently occurs during the first half of the treatment course. This is marked by the appearance of new lesions and a substantial increase in the inflammatory components of existing lesions. The reason for this phenomenon is not yet known, and has been occasionally misinterpreted an indicating treatment failure. Radiation should be continued, uninterrupted, and a complete resolution of all skin lesions usually follows.

Nearly all patients experience excessive dryness of the skin with various degrees of scaling during treatment. Some patients develop erythema and desquamation with doses of > 3000 rads and some develop lower extremity or generalized skin edema with or without bullae. Interruption of the treatment for a few days is usually sufficient to overcome these manifestations of acute radiation morbidity. In more severe cases, short-term topical application of high-potency steroid and/or systemic diuretics may be necessary. Patients who present with total-skin erythema are frequently extremely sensitive to the effects of electron-beam therapy. This must be anticipated, with appropriate adjustment of daily dose, in order to avoid severe desquamation.

Epilation invariably occurs at the end of treatment, but unless the hair follicles have been destroyed by MF, a complete regeneration of the hair usually occurs within 4–6 months after completion of treatment. Anonychosis also occurs in most patients treated without nail shields, but the nails

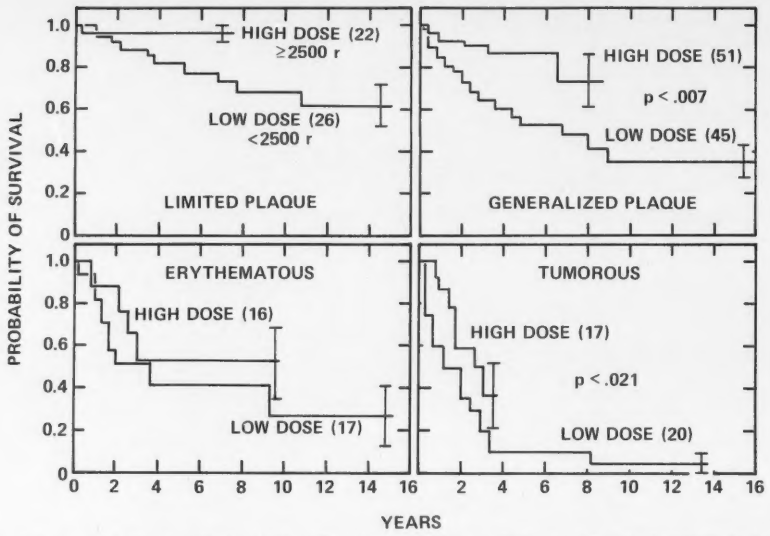

FIGURE 8.—Actuarial analysis (Kaplan-Meier) (19) of survival of patients following the first course of electron-beam therapy as related to initial dose. Low dose = 800–2499 rads, high dose = ≥ 2500 rads. Tests of significance are performed by the generalized Wilcoxon test of Gehan (20).

regenerate within several months after completion of treatment. Most patients develop temporary impairment of sweat-gland function due to radiation injury of the eccrine structure. Sweat tests performed on patients with MF before and after electron-beam therapy have confirmed the presence of anhidrosis in all patients upon the completion of a course of 3000–3600 rads, but there was recovery of sweat-gland function within 6–9 months.[5]

Chronic cutaneous radiation-induced damage is rather unusual. Telangiectasia and other changes of chronic radiodermatitis may be noted in patients after repeated courses of electron-beam radiation or extensive high-dose localized orthovoltage radiation in addition to electron-beam therapy. These changes appear to be especially prevalent among patients who have received lengthy courses of topical chemotherapy in addition to skin radiation, while they are uncommon following a single course of ≤ 3600 rads. Microscopic examination of the skin of patients treated for MF with electron-beam radiation after periods of ≥ 10 years has shown that these are only mild chronic changes after doses of 1000–2800 rads (16). There has been a single report on radiation-induced squamous cell carcinoma of the skin in a patient treated with electron-beam radiation (12).

Nearly all patients with MF respond to the initial course of electron-beam radiation with prompt relief of symptoms, disappearance of the great majority of skin lesions, clearing of skin infections, and healing of skin ulcers even when treated with relatively low doses in the range of 800–2400 rads (17). In many patients total-skin radiation with electrons results in a complete disappearance of all cutaneous lesions (17,18). Figure 7 shows that the probability of complete remission of cutaneous manifestations of MF following the initial course of electron-beam radiation is dose-dependent. Only 18% of the patients treated with doses < 1000 rads responded with complete regression of all skin lesions. In contrast, 90 of 97 (93%) patients treated with high doses (≥ 3000 rads) attained a complete remission. The probability of complete remission also relates to the initial extent of skin involvement (table 1), but within each category, the higher doses were more efficient than the lower doses in eliminating all cutaneous evidence of MF.

The induction of a complete remission is highly desirable since a significant proportion of patients who achieve a complete remission maintain that remission for periods of 4–18 years following the completion of a single course of electron-beam therapy (17,18). Although it is true that the natural history of the disease is exceedingly variable in individual patients (frequently characterized by a slow progression, occasional spontaneous improvement, or brief remission), it seems that the therapy, rather than the natural course of the disease, is

[5]Price NM. The effect of electron beam therapy on eccrine gland function in mycosis fungoides. Submitted for publication to *Archives of Dermatology*.

TABLE 1.—Likelihood of initial complete remission of all skin lesions after 1st course of electron-beam therapy

Extent of skin involvement	Initial dose* (rads)				Totals (%)
	< 1000	1000–1999	2000–2999	≥ 3000	
Limited plaque	1/3	11/15	4/4	21/22	37/44 (84)
Generalized plaque	0/5	13/22	16/24	44/44	73/95 (75)
Erythematous	0/5	4/10	5/7	11/15	20/37 (54)
Lichenoid	0/1	2/2	0/1	1/1	3/5 (60)
Tumorous	2/3	4/13	5/10	13/15	24/41 (59)
Totals (%)	3/17 (18)	34/62 (55)	30/46 (65)	90/97 (93)	157/222 (70)
			120/143 (83)		

*No. of patients with complete remission/No. of patients treated.

responsible for these long-term remissions. Figure 8 shows that for every stage of disease the survival of patients treated with high initial doses of radiation is better than that of patients treated with low doses. This suggests that in many patients, aggressive treatment may modify the natural course of the disease and may, in fact, lead to improved survival and cure. This theory has been disputed, but we firmly believe that aggressive treatment with a curative intent is indicated as soon as the diagnosis of MF is established histologically, even in its earliest forms, and that treatment aimed at the total skin should include high-dose electron-beam radiation.

High-Energy (Supervoltage) Photons

Although complete and durable remissions are often achieved with total-skin electron-beam therapy, many patients relapse within the first 3 years after therapy. In some patients, relapse may result from lack of penetration of the beam into the deeper subcutaneous tissues or from inadequate radiation dose. However, in other patients, relapse may result from re-dissemination of disease into the skin from persisting foci in extracutaneous sites. At the time of the initial diagnosis histologically confirmed extracutaneous involvement is relatively rare; however, more than half of all patients have various degrees of peripheral lymphadenopathy (18). Biopsies from such enlarged lymph nodes usually show proliferation of a benign nature such as dermatopathic lymphadenitis (17). Clinical studies (17) as well as histopathologic and cytogenetic studies (21) have suggested, however, that in MF, unlike other dermatoses, dermatopathic lymphadenitis is not a purely benign condition and may represent the earliest manifestation of disease in lymph nodes. Because of the low penetration of 2.5–7.0-mev electrons, treatment with the electron beam will have no effect on such deeply situated foci of disease, and more penetrating modalities are necessary to eradicate extracutaneous involvement.

For extracutaneous involvement apparently confined to lymph node-bearing areas, total-lymphoid radiation with 4–6-mev photons coupled with total-skin radiation with electrons has been suggested (17,18). Total-lymphoid radiation has been shown to be a safe and effective treatment for Hodgkin's disease and other malignant lymphomas but there have not yet been any reports on its therapeutic effects in MF. At Stanford we have treated three patients with concomitant total-skin electron-beam therapy and total-lymphoid radiation with 6-mev photons. Treatment was well-tolerated in all patients without serious acute or chronic complications. Two of the patients were treated for relapsing disseminated disease and eventually died from generalized MF. One patient has recently been treated as part of an investigational protocol for the treatment of various stages of MF. He presented with generalized erythematous disease and histologically proven dermatopathic lymphadenitis. His treatment program involved 3600-rad total-skin radiation with electrons and simultaneous total-lymphoid radiation to 3000 rads with 6-mev photons, followed by daily topical application of mechlorethamine (20 mg %). The treatment was well-tolerated and the patient has been followed now for 9 months without evidence of recurrent disease. At the present time it is impossible to assess the value of total lymphoid radiation in the treatment of MF, and it should be regarded as strictly investigational. However, the simultaneous administration of total-lymphoid and total-skin radiation is possible as far as technique and tolerance are concerned.

Another treatment which has been suggested for disseminated extracutaneous involvement is frac-

tionated total-body radiation with 4–6-mev photons (18). There is extensive experience with this technique in the management of patients with generalized nodular lymphomas and chronic lymphatic leukemia (22,23). Total-body doses of 10–25 rads are delivered two to three times per week for total doses of 100–150 rads. There have been no reports in the literature indicating the use of such therapy in MF. Recently, however, we treated three patients who had advanced extracutaneous involvement and had failed previous electron-beam and various chemotherapy programs. A full treatment course in these patients was not possible because of bone marrow suppression by previous chemotherapy, and therefore a full assessment of the value of treatment could not be made. Further studies in more patients are obviously necessary, but this treatment modality may be of value in patients with extracutaneous and extralymphatic involvement.

Another modality with therapeutic potential in MF is sequential half-body radiation, reported as an effective palliative treatment for metastatic disease (24). In this technique, one half of the body is treated with a single dose of 600–1000 rads given with high-energy photons followed by a similar dose to the other half of the body 3–6 weeks later when hematologic recovery has occurred. In view of the known radiosensitivity of MF lesions to high-dose single-fraction radiation, this approach would seem ideal for patients with extensive cutaneous and extracutaneous involvement. However, due to serious toxic effects with this regimen, it should be used as an investigational technique *only*. More experience will be necessary before it could be recommended for routine use.

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Once Weekly Total-Skin Electron-Beam Therapy for Mycosis Fungoides: 7 Years' Experience

Lourdes Z. Nisce* and Bijan Safai [1]

SUMMARY

A total of 115 patients with mycosis fungoides were given total-skin electron-beam therapy (TSEB), utilizing 3.5-mev electrons at doses of 400 rads to the entire skin surface once a week for 6–8 consecutive weeks. Prompt relief of symptoms and regression of lesions were observed in all patients. Of the 81 patients at risk for 12–91 months (median, 24 months) following TSEB, initial unmaintained remissions lasted 6–69 months (median, 19 months). No untoward immediate or late effects have been noted in the bone marrow or normal skin which was irradiated. The duration of remission following TSEB correlated well with lymphocyte responsiveness to various mitogens and antigens, but not with the initial response. Thymic hormone factor levels (Facteur Thymic Serique) were elevated in the majority of these patients with mycosis fungoides.

[Cancer Treat Rep 63:633–638, 1979]

The radiosensitivity of all of the classic cutaneous lesions of mycosis fungoides (MF) including plaques, nodules, and ulcers is well-documented. Because of the sharply limited penetration of the electron beam, it has been increasingly employed in the treatment of MF and of other cutaneous malignancies involving extensive segments of the body.

Since 1953 (1), various techniques and dose regimens (2–5) have been employed in irradiating the entire skin surface with high-energy electrons. At our hospital, we have used 2.5- and 3.5-mev electron-beam therapy from a Clinac 6-mev linear accelerator employing a once weekly fractionation scheme. The technique and dosimetry (6,7), clinical advantages, rationale, and our early experience were reported previously (7,8).

TECHNIQUE AND DOSIMETRY

Briefly, patients are treated in the upright position employing four fields, namely, anterior, posterior, and both laterals, which are all irradiated during each session, once weekly for 6–8 consecutive weeks. The earlier group was treated with 400 rads for six sessions, but recently the course has been increased to eight sessions. The depth dose curve of the 3.5-mev electrons is shown in figure 1. Currently, the bremsstrahlung is 0.5%, which is lower than that of our previous reports (6,7) and those of others (8).

The standard dose given for each weekly session is 400 rads to the posterior and anterior fields and 200 rads to each of the lateral fields for four sessions. The loading dose is reversed (ie, 200 rads to the anterior and posterior fields and 400 rads to each lateral field) for two sessions. This results in a relatively homogeneous dose distribution across the entire circumference of the body as shown in figure 2. With our currently employed technique of eight weekly sessions, the anterior and posterior surfaces receive 400 rads for five sessions and the lateral surfaces receive 400 rads for three sessions. The dose distribution is very similar to that shown in figure 2. This has been well-tolerated and has produced more durable remissions when compared to our lower dose regimen.

Local electron-beam radiation, 6–10 mev from the Betatron, is routinely employed for the self-shielded and underdosed areas such as the vertex, soles, perineum, shoulders, and inframammary areas in the females. Once weekly doses of 400–500 rads for three to four sessions are usually sufficient, depend-

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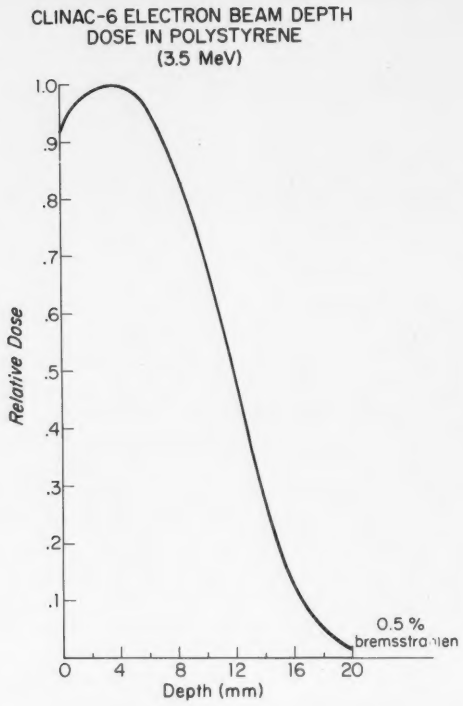

FIGURE 1.—Depth dose curve for 3.5-mev electrons.

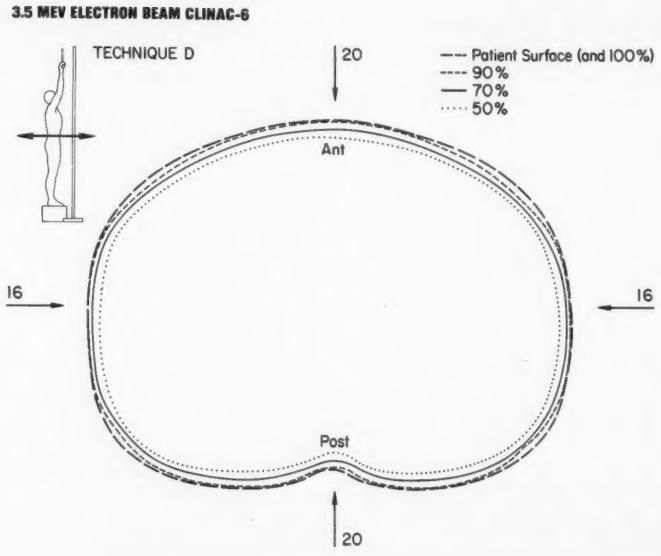

FIGURE 2.—Composite dose distribution from a 4-field technique. Dose ratio is as follows: anterior and posterior fields, 400 rads, and both laterals, 200 rads, for each weekly session × 4 (standard dose); and anterior and posterior, 200 rads, and both laterals, 400 rads, for each weekly session × 2 (loading dose). Time of reversal of dose ratio is flexible depending on the relative severity and extent of lesions and/or skin reactions.

TABLE 1.—Characteristics of MF patients receiving TSEB*

No. of patients	
Total treated	115
Evaluable	109
Median mos at risk (range)	18 (6–91)
No. of males/females	69/40
Median age in yrs (range)	61 (30–95)

*Total population treated from Feb 1971 to Sept 1978.

ing on the severity of the lesions. Appropriate shielding of nails, lenses, and male genitals is carried out when indicated as described previously (7).

MATERIALS AND METHODS

Since February 1971, 115 patients with biopsy-proven MF have been treated with this technique. Six patients did not complete the course because of various reasons not related to treatment and therefore a total of 109 patients are evaluable. The age and sex distribution is shown in table 1. Ages ranged from 30 to 95 years (median, 61 years). There were 69 males and 40 females. The median followup is 18 months following the initial total-skin electron-beam therapy (TSEB) (range, 6–91 months).

Virtually all of the patients (103 of 109 [94%]) had generalized skin involvement when they were first referred for TSEB, as shown in table 2. Most patients (90%) had been previously treated elsewhere with various topical or systemic chemotherapeutic agents, steroids, ultraviolet irradiation, and/or local irradiation. Palpable lymphadenopathy was found in 99 of 109 (91%) patients.

Palpable lymph nodes were not routinely biopsied unless they were highly suspected to be involved with MF. Most often, biopsies of even the clinically suspected nodes were reported as dermatopathic lymphadenitis. Bipedal lymphangiograms were done whenever feasible. However, since practically all patients had widespread infected cutaneous lesions, lymphangiography was occasionally deferred until the infection had completely resolved, sometime after the third session or at completion of TSEB.

TABLE 2.—Pretreatment characteristics of MF patients receiving TSEB*

	No. of patients (%)
Generalized skin involvement	103 (94)
< 90% skin involved	7 (6)
Lymphadenopathy	99 (91)
No lymphadenopathy	10 (9)
Previously treated elsewhere	98 (90)

*Total of 109 patients followed for 6–91 mos (median, 18 mos) from Feb 1971 to Sept 1978.

RESULTS

Complete regression (CR) of the various cutaneous lesions was obtained in all of the patients. Usually after the second or third session, itching, scaling, and erythroderma were significantly diminished. The skin nodules were flatter and even the bleeding ulcerated lesions started to show early epithelization.

Table 3 shows the duration of remission following the first course of TSEB. CR lasted for a median of 9 months (range, 6–69 months) in the 109 patients followed for 6–91 months (median, 18 months) compared to a median CR duration of 19 months (range, 6–69 months) in the subgroup of 81 patients followed for a minimum of 12 months (range, 12–91 months).

Disease recurred in 31 of 81 patients at risk for a minimum of 12 months following TSEB at various intervals ranging from 6 to 18 months. Analysis of recurrences showed the following:

(*a*) There were six recurrences in the earliest series of 11 patients who received treatment to only the anterior and posterior fields to total doses of 200–300 rads for three or four sessions. At 9–14 months, disease recurred at the flanks which received less radiation than the anterior and posterior surfaces. One of the six patients had a 20-year history of disease and died of septicemia 14 months after the initial TSEB. The other five patients received a second course of TSEB limited only to the lateral fields resulting in a second remission lasting 8–16 months. Two of the five patients ultimately died of leukemia shortly thereafter, one died of a cardiovascular accident, one died with rectal carcinoma, and the fifth was lost to followup.

(*b*) All of the patients with short-term remissions had very advanced disease manifested by palpable lymphadenopathy combined with varying severity

TABLE 3.—Duration of remission in MF patients after initial TSEB

	Total population with 6+ mos of followup	Subgroup with 12+ mos of followup
No. evaluable	109	81
Median—		
Mos at risk following TSEB (range)	18 (6–91)	24 (12–91)
Mos of remission (range)	9 (6–69)	19 (6–69)

TABLE 4.—Prognostic factors of 81 MF patients at risk for 12–91 mos (median, 24 mos) after TSEB

Factor	No. of patients treated	Median mos at risk (range)	No. of patients with response	Median mos of remission (range)	Disease status
No lymphadenopathy	10	45 (14–69)	10 (excellent)	45 (14–69)	All patients alive with no evidence of disease
Erythroderma in various combinations with plaques, nodules, and ulcers	20	24 (12–48)	15 (excellent), 5 (good)	10 (6–31)	14 patients had disease recurrence at 6–18 mos, 5 died at 12–24 mos, and 5 have no evidence of disease at 14–31 mos

and extent of plaques, nodules, and ulcers. Of these, four patients had positive lymph node biopsies.

(*c*) The additional findings of circulating Sézary cells invariably resulted in even more transient remissions lasting no more than 6–8 months, with only one of seven patients barely completing 1 year of significant remission.

Of the 25 patients who were treated with the four-field technique to doses of 400 rads for six sessions, the time to recurrence following the initial TSEB was 6–18 months. Fifteen of the 25 patients received a second course of TSEB and a second remission was obtained lasting 8–24 months at the time of data compilation. Some patients required sporadic local electron irradiation to underdosed areas, most often to the extremities. All of the other ten patients had Sézary syndrome and/or erythroderma and were further treated at the originating institutions with various chemotherapeutic agents and other modalities.

DISCUSSION

Our patient population is characterized by a fairly advanced stage of the disease when first referred for TSEB; 91% had clinical lymphadenopathy and 94% had generalized skin involvement. However, all of the patients were able to lead a relatively normal life after the initial two or three sessions so that the once weekly journey to the radiation therapy department did not interfere with their daily activities. In the series of Grollman et al (4), excellent results of TSEB for MF are defined as "complete clinical remissions sustained for at least six months." No patients survived for 1 year without disease recurrence. In our series of 81 patients at risk for 12–91 months following initial TSEB, ten remained free of disease for periods ranging from 14 to 69 months. Twenty-two of the 56 patients with CR in the TSEB series of Fuks and Bagshaw (3) had limited disease and the rest had advanced disease. In contrast, 90% of our patients were in the advanced stages. In their group, all recurrences occurred within the first 3 years after TSEB. None of the eight patients who remained free of disease 3–11 years after their initial treatment had tumorous disease or generalized plaques. In analyzing our 81 patients at risk for 12–91 months we identified two clinical prognostic factors (table 4). The absence of clinical lymphadenopathy, regardless of extent and severity of plaques, was associated with long-term remissions. There were only ten (12%) patients in this group and all are alive and free of disease at 14–69 months (median, 45 months). In the other extreme are 20 patients with erythroderma in addition to plaques, nodules, and ulcers of varying severity. Although 15 patients obtained excellent response, the duration of remission was rather short (median, 10 months; range, 6–31 months). More than two thirds of the patients (14 of 20) had disease recurrences within 6–18 months; five of 20 died with disease at 12–24 months and five have been free of disease for 14–31 months.

In order to correlate the immunologic state of the patient with the clinicopathologic features and response to therapy, we undertook a small pilot study of 11 consecutive patients. The most interesting observation is the close correlation between the response to electron-beam therapy and the patients' lymphocyte responsiveness to various mitogens and antigens, including phytohemagglutinin, concanavalin A, pokeweed mitogen, *Candida*, *Escherichia coli*, *Staphylococcus*, and purified protein derivative. Table 5 describes the clinical features, results of node biopsies, lymphangiograms, and lymphocyte response to various mitogens and antigens. This clearly indicates that there is a close correlation between the lymphocyte responsiveness and the duration of remission. When the lymphocyte response was moderate (patients 6–8) or very low

TABLE 5.—Clinical features, biopsy and lymphangiogram results, and lymphocyte response to mitogens and antigens in MF patients receiving TSEB

Patient No.	Lesions*	Lymph node biopsy†	Lymphangiogram†	Lymphocyte response to mitogens and antigens†							Duration of remission‡
				Phytohemagglutinin	Concanavalin A	Pokeweed mitogen	*Candida*	*Escherichia coli*	*Staphylococcus*	Purified protein derivative	
1	PN	ND	ND	N	M	N	N	M	M	–	14 mos, NED
2	PNL	Dermatopathic	–	N	N	N	N	N	N	+	18 mos, NED
3	PNUL	Dermatopathic	+	N	N	N	N	N	N	+	12 mos, NED
4	PNUL	Dermatopathic	+	N	M	N	N	M	M	–	18 mos, NED
5	PNUL	MF	–	M	N	N	ND	ND	ND	ND	12 mos, NED
6	PNUL	Dermatopathic	+	N	L	L	N	M	L	+	Recurrence at 10 mos
7	PNUL	ND	ND	ND	ND	ND	M	L	L	+	Recurrence at 6 mos
8	PNUL	ND	+	M	N	N	L	L	L	+	Recurrence at 8 mos
9	PNUL	MF	ND	L	L	L	N	L	M	+	Died of lymphoblastic leukemia
10	PNUL	MF	+	L	L	L	L	L	L	+	Recurrence at 8 mos
11	PNUL	Dermatopathic	+	M	L	L	L	L	L	–	Recurrence at 6 mos

*P = plaques; N = skin nodules; U = ulcers; L = clinical lymphadenopathy.
†ND = not done; + = positive; – = negative; N = normal; M = moderately low; L = very low.
‡NED = no evidence of disease.

(patients 9–11), we observed that skin lesions recurred within a short period (6–10 months). This is in contrast to the other five patients studied who exhibited relatively normal lymphocyte responsiveness and have remained free of cutaneous recurrence for ≥ 12 months. There was complete healing of the various cutaneous lesions (plaques, nodules, and ulcers) in all of these 11 patients, regardless of the patients' lymphocyte responsiveness. Therefore, at this time, we cannot use the degree of lymphocyte responsiveness to predict the response to TSEB. The studies were usually repeated 2–3 months after TSEB and at various intervals during the course of the disease. Early observation in this group showed no change in the lymphocyte responsiveness immediately following a full course of TSEB. Additional data on long-term lymphocyte responsiveness are being accumulated for this group of patients as well as for all patients before their initial TSEB.

Our initial observation on the thymic hormone factor levels showed an elevation in the majority of MF patients, as has been described previously (10). This increase in thymic hormone, especially in elderly MF patients whose thymus glands are involuted, indicates an abnormal finding. The significance of this abnormality is not known at this time; further investigation is underway. However, these levels have remained unchanged following TSEB.

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Electron-Beam Therapy in England

Margaret F. Spittle [1,2,*]

SUMMARY

Since 1962, total-skin electron-beam therapy has been available in London, England, for the treatment of patients with mycosis fungoides and skin lymphomas. The 6-mev linear accelerator produces a pencil beam of electrons at 7 mev, which are scattered through a brass scatterer and decelerated by either of two carbon decelerators or a copper decelerator to produce a beam of effective energy of 2.5, 3, or 3.5 mev; these beams have an 80% isodose distribution at 5.5, 8, and 11.5 mm, respectively. The patient receives 200 rads to the anterior, posterior, and right and left lateral fields, for a total dose of between 1600 and 2600 rads in ten treatments over 5–7 weeks. Complete clearing of the disease can be predicted in all patients except those with the most advanced tumors. However, the duration of remission after electron-beam therapy is approximately 18 months and we are presently investigating the combination of psoralens and ultraviolet light therapy as maintenance treatment following lower-dose electron-beam therapy.

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Total-skin electron-beam therapy has been available in London, England, since 1962. The advantages of this therapy have been described by Trump et al (1) and Bagshaw et al (2). Szur et al (3) described the method by which the electrons produced at 8 mev were slowed down by carbon decelerators to produce a beam with an 80% depth dose at 4.5 or 6.5 mm. The AE1 6-mev linear accelerator installed at the Hammersmith Hospital (London, England) in 1969 was also modified to treat skin lymphomas, particularly mycosis fungoides. More than 100 patients have been treated with this newer machine, most of them having been referred from my colleague, Dr. P. D. Samman, at the joint clinic at St. John's Hospital for Diseases of the Skin (4). The pencil beam of radiation produced is diffused by passing it through a brass scatterer. This method was found to produce less X-ray contamination than the use of the gold scatterer (5). Although X-ray contamination of the beam is 6% within the treatment cone, the patient is centered outside this X-ray field and the contamination is, therefore, reduced to $< 1\%$.

Although electrons are produced at 7 mev, the equivalent of approximately 0.5 mev of energy is absorbed in the interposed air between the patient and the source. One copper and two carbon decelerators have been devised to reduce the energy of the beam further to effective voltages of 3.5, 3, and 2.5 mev, respectively. The 7-mm carbon decelerator produces electrons with the 80% depth dose at 5.5 mm, the 4-mm carbon decelerator produces electrons with the 80% depth dose at 8 mm, and the 0.3-mm copper decelerator produces electrons with the 80% depth dose at 11.5 mm.[3] In recent years, the more penetrating beams have been those most frequently employed.

As the patient stands to one side of the main axis of the beam there is a dose gradient across the field and dosimeters on each side of the treatment area record a 7.5% falloff across this region. The patient is rotated towards the source of electrons rather than facing down the main axis of the room. The

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[2]My thanks are due to Dr. Peter D. Samman at St. John's Hospital for Diseases of the Skin and my predecessor the late Dr. Leon Szur who have allowed me to become interested in this group of patients, A. Beck for her help in treatment, David Hare for his advice, and Judith Leach for her secretarial assistance.

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[3]Alderton A. Personal communication, 1976.

isodose lines are vertical to a level of 2.5 meters which is adequate for treatment. The machine is set to irradiate horizontally and the patient stands 6 meters from the machine displaced laterally by 1.3 meters from the main axis of the X-ray beam. Isodose perturbation at ground level is avoided by placing the patient on an 8-cm platform. A disposable gown is worn and lead glass goggles are added if the head is also to be treated. To protect the testes, an 11-cm wax shield is used; this is lined with 3 mm of lead to absorb the bremsstrahlung from low atomic number material. If the head is not to be treated, a 15-mm thick perspex shield is placed at the appropriate level. Any shielding of other parts, for example, previously heavily treated small areas, may be undertaken using an especially tailored block board.

The patient is treated four times weekly. Both the anterior and posterior fields are treated on Days 1 and 3 and the right and left lateral fields are treated on Days 2 and 4. On each occasion, a 200-rad dose is administered; this is recorded as a total of 200 rads when all four fields have been treated once. Initially, the treatment doses achieved were approximately 1000 rads and gradually this dose has been increased, with patients receiving up to 2600 rads in ten treatments over a 5–7-week period. Lithium fluoride dosimetry has shown that the extent of overlap of these fields is such that when the anterior, posterior, and right and left lateral fields have each been treated once with a given dose of 200 rads, approximately 400 rads are received by most of the skin. It is important to note that at the Hammersmith Hospital patients are recorded as receiving 200 rads when each of the four fields has been treated once to 200 rads. Therefore, the total dose expressed for a full course of X-ray treatment ranges between 1600 and 2600 rads when each area of skin has in fact received approximately double this dose.

It is inevitable that when treating the whole of the skin some area will be shielded from the beam in some treatment positions. Topping-up doses to the axillae, the undersurfaces of the feet, and the perineum are frequently needed to ensure uniformity. This can be given with X-rays in the 80–100-kv range. The epiphora which is commonly due to infiltration of the eyelids with mycosis fungoides can be treated by using an internal lead eye shield with superficial X-rays given to the areas covered by the lead spectacles used for the electron-beam therapy.

Generalized erythema and desquamation are seen after the treatment is completed; these effects vary in severity between patients and are most severe in those who exhibit extensive disease initially. In these patients, it is often impossible to achieve the full dose, and protracted intervals in treatment time may be necessary. Pigmentation, ankle edema, and gynecomastia are frequently seen. Fingernails and toenails are always shed 1–3 months following therapy and good regrowth of the nails is seen. Temporary alopecia occurs when the head is treated. Where follicular mucinosis has destroyed the hair follicles, patches of permanent alopecia remain. Bilateral brawny ankle edema may be troublesome in older patients, particularly if a lymphangiogram has been recently performed.

In other centers, total-skin electron-beam therapy has been attempted using different modifications of the linear accelerator. At the Middlesex Hospital, Planskoy[4] has devised a two-field technique, treating fields 42 × 42 cm with scattered 5-mev electrons. The patient is placed at a 10° horizontal angle, thus receiving an increased dose in the lateral regions. An electron beam is produced with an 80% depth dose at 13 mm, and, if a gap of 8 cm is left between the two large fields, a homogenous dose distribution is achieved across the anterior surface of the patient. To reduce the depth dose, a cotton sheet may be placed over the patient.

In the Manchester center in England, the patient is placed on a treatment couch which moves under the electron beam on tracks, and again good uniformity of dose is achieved. The treatment may be fractionated, as convenient, locally and 600 rads once weekly may be repeated on two occasions to achieve useful disease response in patients with advanced disease.

Since 1964 in Cambridge, England, an apparatus utilizing the mono-energetic 2.2-mev electron beta-ray emitted from strontium 90 has been utilized to treat patients with very superficial mycosis fungoides (6). Unfortunately, the 90% depth dose is as superficial as 1 mm, and, therefore, only early disease may be treated and the duration of remissions is not long. The strip of strontium 90 traverses the length of the couch giving 50 rads to the patient's skin on each traverse. On each occasion, 200 rads are given to the anterior, posterior, and right and left lateral surfaces, and the treatment is repeated until 2000 rads are given in ten treatments over 12 days (7). The extreme simplicity of this unit has much to recommend it, but, as with all the other whole-skin irradiation methods, there is considerable lack of uniformity.

RESULTS

At St. John's Hospital for Diseases of the Skin we have found the long-term effects of electron-beam

[4]Planskoy B. Personal communication, 1978.

therapy for mycosis fungoides to be less impressive than the results reported from Stanford University (Calif) (8), although we have some patients who have been in remission for > 7 years. We tend to treat the more advanced cases where the average duration of remission following electron-beam therapy has been approximately 18 months. The patients who have been treated with electron-beam therapy for minimal disease have remained clearer for longer periods and there is certainly a dose-related response. A patient who received an overdose of electrons because of a mechanical fault achieved complete clearance of disease in the areas which received the overdose whereas persistent disease remained in those areas that had had only minimal electron-beam therapy.

Although we have patients with tumors who have remained completely disease-free for > 2 years after electron-beam therapy, the disease usually recurs within 2–6 months after therapy in these advanced cases. In our experience it is unusual for a patient to be cured permanently by electron-beam therapy, although we do have two patients who have remained disease-free for 10 years and who initially had widespread skin involvement. Although initial relapse following the treatment tends to occur in areas which had received low doses, for example, the groins and axillae, the general recurrence which follows does not necessarily seem to spread from those areas but appears to be recrudescence of the disease in all sites.

Approximately 1 year after the completion of radical electron-beam therapy, many patients exhibit telangiectasia, especially on the anterior surface of the trunk, the root of the penis, and the elbows. Although the cosmetic deformity is minimal, we are anxious that these patients may have impaired long-term functional capability of the skin. One patient with extremely extensive disease developed small painful necrotic ulcers over the whole of the anterior trunk. This occurred at the same time as recurrence of the disease to which the patient rapidly succumbed. The dose achieved in these patients seems to be the maximum tolerated by the whole skin when this fractionation schedule is used.

We are not impressed by the high incidence of nodal involvement in mycosis fungoides although our policy has been to perform routine lymph node biopsies (9). Approximately one half of our patients eventually die as a result of the accompaniments of skin ulceration and most of the others die of unrelated causes.

Recently, the advent of long-wavelength ultraviolet irradiation in conjunction with 8-methoxypsoralens therapy (PUVA) has affected the treatment of most cases of mycosis fungoides (10). Patients with superficial disease; no matter how extensive, are no longer given electron-beam treatment until they have failed to respond to PUVA therapy. Again, some areas do not receive adequate treatment from the ultraviolet light, and occasional nonulcerated infiltrated dermal nodules appear. Local supplementary treatment with low-dose superficial X-ray therapy is given. The peri-orbital regions shielded from PUVA may also be treated by low-voltage X-rays using external eye shields.

It is our policy now to give PUVA therapy initially to all cases of superficial mycosis fungoides in view of the general well-being of the patient attendant upon this form of treatment. Those areas which appear to be too deeply infiltrated to be reached by PUVA treatment are then topped-up by local X-rays. Electron-beam therapy is now reserved only for those patients presenting with tumors where PUVA is ineffective. In some patients initially cleared of advanced disease by electron-beam therapy, the remission has been prolonged using maintenance PUVA. This is now our policy with extensive disease. The disadvantages of repeated ultraviolet light therapy will probably include the induction of skin malignancy. When all the long-term effects have been adequately documented, the place of photochemotherapy and electron-beam therapy for the treatment of mycosis fungoides can be adequately evaluated.

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Amphotericin B Effects in Tissue Culture Cell Lines

Jerome B. Block,* William Isacoff, and Marian Dietrich [1]

Mycosis fungoides is often clinically characterized by a rapid response to a variety of anticancer drugs with subsequent relapse. We have been examining potential drug adjuvants which may offer enhanced tumor cytotoxicity. In this paper we present some early in vitro data with amphotericin B on various tumor cell lines which may have relevance to future clinical studies in mycosis fungoides.

MATERIALS AND METHODS

Culture Lines

L1210 mouse leukemia, 6410 human myeloid leukemia, and SHG, a human melanoma cell line derived from malignant ascites, were grown in tissue culture and used for all experiments. The cells were grown in 15-ml tissue culture flasks (Falcon Plastics, Los Angeles, Calif) at an initial concentration of 1×10^5 cells/ml using RPMI-1640 medium (GIBCO, Grand Island, NY) that was supplemented with 15% fetal calf serum which had been heat-inactivated for 1 hour at 56°C, and 1% penicillin and streptomycin solution (GIBCO). Cultures were maintained at 37°C in an atmosphere containing 5% CO_2 and 95% air. Cells for study had been transplanted at a median initial concentration of 1×10^5 cells/ml twice a week, usually on primary culture Day-3 and -4 sequences prior to experimental study.

Experimental Procedure, Media, and Drug Preparation

Each experimental point was derived from three cultures. Experiments were done in 15-ml tissue culture flasks (Falcon Plastics). The flasks were first gassed with 5% CO_2 in air for 15 seconds to reflect experimental incubator conditions. Four ml of RPMI-1640 medium was added initially to each tissue culture flask. This was often done the day before the experiment; the flasks were kept overnight at 4°C, since such a procedure will detect any cracks in the culture flask because the resultant loss of CO_2 causes a pH change in the medium with an alteration in indicator color.

Cell Preparation

Cells were grown $1^1/_2$ days prior to use in a "mother" or primary culture flask. Cell counts were taken after abrupt flask agitation to diffuse any clumps into single cells. Cells were diluted with fresh complete medium to a count of 1×10^6 cells/ml. One-half ml of this cell concentration was added to a tissue culture flask so that the final cell concentration was 1×10^5 cells/ml at the start of the study. The cultures were then placed in the incubator and this experimental point was termed Day 0. All cell counts were done on a Coulter Model F on Days 0, 4, and 7 of growth. Cells were re-fed without drug with 1 ml of fresh RPMI-1640 supplemented medium on Day 4 after the cell count was taken. Experiments were incubated at 37.5°C in a 5% CO_2 and 95% air atmosphere. Sterile conditions were adhered to throughout the experiment. Trypan-blue dye exclusion was used to verify initial cell viability for all studies. Log growth cultures represented those transplanted from the "mother" culture when cell counts in the culture were at 100,000/ml. Lag growth cultures represented those transplanted from the "mother" culture when the cell count had risen to 3,000,000/ml.

Cell cultures were grown for 7 days with analysis of cell numbers on the first, fourth, and seventh day of culture.

RESULTS

Table 1 shows the effects of amphotericin B drug concentration on L1210 growth in the Day-4 and -7 culture cell counts. In both log and lag growth culture transplants, the drug inhibited L1210 growth at concentrations of ≥ 8.2 μg/ml. Log growth cultures are the more sensitive to the cytotoxic effects of amphotericin B as evidenced by inhibited growth in the Day-4 culture at 4.6 μg/ml and the failure of the log cultures to regain normal cell counts by Day 7 at an amphotericin B concentration

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TABLE 1.—Effects of amphotericin B on L1210 leukemia in vitro

Amphotericin B concentrations (μg/ml)	Cell counts* × 10^3/ml³ (Day 4)		Cell counts* × 10^3/ml³ (Day 7)	
	Log growth transplants	Lag growth transplants	Log growth transplants	Lag growth transplants
0	35,937	33,252	35,427	32,333
1.0	40,817	37,431	37,047	36,356
2.8	34,647	38,335	38,335	35,883
4.6	16,786	26,336	39,899	39,353
8.2	2737	6797	5144	32,441
10.0	2475	3677	2876	17,200
28.0	3198	3582	3832	3527

* Mean of 3 cultures.

TABLE 2.—Interactions between amphotericin B and DTIC on a human melanoma cell line in vitro

Culture group	Drug concentrations (μg/ml)		Cell counts* × 10^3/ml³
	Amphotericin B	DTIC	
A	0	0	33,779
	8.2	0	32,385
	10.0	0	28,630
	28.0	0	5020
B	0	0.2	31,729
	0	1.3	29,813
	0	2.0	24,338
	0	9.2	7114
C	28	0.2	4657
	28	1.3	4423
	28	2.0	4431
	28	9.2	4081
D	10	0.2	12,541
	10	1.3	8423
	10	2.0	7569
	10	9.2	7054
E	8.2	0.2	23,823
	8.2	1.3	13,216
	8.2	2.0	7320
	8.2	9.2	6828

* Mean of 3 cultures analyzed on the 7th day of culture. All culture groups (A–E) were done simultaneously as part of a single experimental study.

of 8.2 μg/ml; lag cultures had regrown to control levels by Day 7 at a similar drug concentration.

Studies with the 6410 human leukemia line and the SHG melanoma cell line gave similar results when amphotericin B was used in log growth cultures. The 50% growth inhibition was similar for all culture lines studied and approximated 5–10 μg/ml of amphotericin B.

Table 2 shows the interactions between amphotericin B and the anticancer drug DTIC on a human melanoma cell line. Culture group A shows the growth inhibitory influence of amphotericin B, culture group B shows the effects of DTIC used singly, and culture groups C–E demonstrate the interactions between DTIC and various fixed concentrations of amphotericin B. In culture groups D and E it is readily apparent that cytotoxicity was induced when nontoxic drug combinations were combined. Thus, 10 or 8.2 μg of amphotericin B which is not toxic to L1210 (culture group A) will produce appreciable growth inhibition when combined with DTIC (culture groups D and E) at concentrations of 1.3 and 2.0 μg/ml, which are not toxic by themselves (culture group B).

In other drug studies in L1210 leukemia and melanoma, we have noted similar enhanced cytotoxicity of amphotericin B with the drugs methotrexate, 5-fluorouracil, and adriamycin. The effects of amphotericin B seem greatest when combined with DTIC or 5-fluorouracil.

DISCUSSION

These observations on amphotericin B suggest application to clinical trials. The concentrations of amphotericin B with cytotoxic in vitro effects are comparable to those reached in plasma during clinical antifungal therapy with amphotericin B (1,2). Presant et al (3) and Krutchik et al (4) have begun evaluation of amphotericin B used in clinical cancer trials as an adjuvant to established chemotherapy. High parenteral doses of 15–30 mg/day of amphotericin B may be safely given if attention is paid to clinical hydration and an induced diuresis to prevent nephrotoxicity. In view of the high response rate of mycosis fungoides to a variety of anticancer drugs, the disease may be suitable for clinical trials with amphotericin B drug combinations in an effort to influence completeness of response and survival prolongation.

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Combination Chemotherapy for Mycosis Fungoides: A Southwest Oncology Group Study [1]

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SUMMARY

Between 1972 and 1977, the Southwest Oncology Group studied the following three chemotherapy programs for the treatment of patients with advanced forms of mycosis fungoides: (*a*) cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) (seven patients); (*b*) adriamycin, vincristine, and prednisone (HOP) (five patients); and (*c*) cyclophosphamide, vincristine, prednisone, and bleomycin (COP plus bleomycin) (12 patients). Among the 24 evaluable patients there was an overall objective response rate of 95% with seven (29%) achieving a complete remission. With the adriamycin-containing chemotherapy, five (42%) of 12 patients achieved a complete remission compared to two (17%) of 12 patients treated with COP plus bleomycin. The median duration of remission (partial plus complete) was longer with the COP plus bleomycin combination (median, 47 weeks) than with the adriamycin-containing combinations (median, 22 weeks; $P = 0.03$). The median survival for all 24 evaluable patients was 95 weeks and was similar regardless of remission-induction therapy. In summary, combination chemotherapy proved to be effective palliative therapy for advanced mycosis fungoides.

[Cancer Treat Rep 63:647–653, 1979]

Mycosis fungoides (MF) is a rare T cell lymphoma which has attracted considerable interest because of its unusual clinical and pathologic features (1–4). Despite the long natural history of MF, most patients eventually develop extensive skin tumors, lymph node involvement, and extranodal involvement requiring systemic chemotherapy. Because of the rarity of MF, there has been little published information regarding the results of combination chemotherapy for MF although this tumor has appeared to be sensitive to single-agent chemotherapy (3).

Since 1972, the Southwest Oncology Group (SWOG) has employed combination chemotherapy for patients with advanced MF and this paper describes our experience with three different drug regimens.

PATIENTS AND METHODS

Between 1972 and 1974 patients with recurrent advanced MF were registered in SWOG study 7204 and were randomized to treatment with either a four-drug chemotherapy program consisting of 750 mg/m² of cyclophosphamide, 50 mg/m² of adriamycin, and 1.4 mg/m² (maximum, 2 mg/dose) of vincristine, all given iv on Day 1, and 100 mg/day of prednisone given orally × 5 days (CHOP) or a three-drug program consisting of 80 mg/m² of adriamycin and 1.4 mg/m² of vincristine, both given iv on Day 1, and 100 mg/day of prednisone given orally × 5 days (HOP). In general, each of these two treatment programs was administered every 3–4 weeks. Once

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patients achieved complete remission (CR) three additional consolidation courses of the same combination were given and then the patients were assigned to receive maintenance therapy consisting of either 200 mg/m² of cyclophosphamide given orally × 5 days, 1.4 mg/m² of vincristine given iv on Day 1 (maximum dose, 2 mg/injection), and 100 mg/day of prednisone given orally × 5 days (COP) or 80 mg/m² of cytosine arabinoside × 5 days divided into every-6-hour sc doses and vincristine and prednisone at the same dose and schedule as used in COP (this program was known as OAP). Maintenance therapy was to be given for 18 months and, if the patients continued in CR, all treatment was to be discontinued thereafter. Thus, in this protocol patients received variable numbers of courses of the remission-induction treatment followed by long-term maintenance treatment if they achieved CR. The total dose of adriamycin was not to exceed 550 mg/m² in this study. The details of this program as it was used for patients with non-Hodgkin's lymphomas can be found elsewhere (5).

Between 1974 and 1977 all patients with recurrent advanced MF were registered in SWOG study 7426. Because the number of patients registered over 2 years in study 7204 was small, all patients in this later study were scheduled to receive the same treatment program consisting of 125 mg/m²/day of cyclophosphamide given orally × 14 days, 1.4 mg/m² of vincristine given iv on Days 1 and 8 (maximum dose, 2 mg/injection), 100 mg/day of prednisone given orally × 5 days, and 4 units/m² of bleomycin given iv on Days 1 and 8 (COP plus bleomycin). Courses of COP plus bleomycin were repeated every 28 days. Remission induction consisted of eight courses of chemotherapy initially; if patients failed to achieve a CR after eight courses of treatment, three additional cycles of COP plus bleomycin were administered.

Criteria for eligibility of patients for these two studies included the following: (*a*) no prior systemic chemotherapy; (*b*) pathologic diagnosis of MF; and (*c*) advanced or recurrent forms of MF with at least extensive plaques, skin nodules, gross skin tumors, lymph node involvement, or extranodal sites of involvement. A pre-treatment workup included chest roentgenograms, bone marrow biopsies, lymphangiograms, and optional lymph node biopsies. Other tests were performed as clinically warranted to assess the extent of disease. Serial evaluations of measurable tumor were performed with each course of treatment. Responses were defined as follows. CR was a total disappearance of all measurable signs and symptoms of MF and partial remission (PR) was at least a 50% regression of all measurable disease lasting for at least 1 month. In general, repeat lymph node biopsies or skin biopsies were not performed in patients who achieved a clinical CR.

Survival and disease-free survival were calculated from the time chemotherapy began by the method of Kaplan and Meier (6). Statistical comparisons of various survival parameters in relation to clinical findings and treatment, as well as the relation of disease-free survival to clinical findings and treatment, were performed by the modified Wilcoxon test of Gehan (7).

RESULTS

Twenty-eight patients were registered in this study but four were not eligible upon review: three because they were felt to have malignant lymphomas other than MF on pathology review and one because of prior systemic chemotherapy. Of the remaining 24 patients, all could be evaluated for response and survival as well as toxicity. The clinical features of these 24 evaluable patients are detailed in table 1. There was essentially no difference in the distribution of clinical features for the 12 patients in each of the two studies.

The overall results for the 24 evaluable patients are summarized in table 2. Seven (29%) patients achieved a CR and the overall objective response rate was 95%. Only one patient failed to achieve at least a PR. Patients receiving either one of the adriamycin-containing regimens (CHOP or HOP) more often achieved CR: five (42%) of 12 patients

TABLE 1.—Clinical features of MF patients

Clinical features	Treatment	
	CHOP-HOP	COP + bleomycin
Total No. of patients	12	12
Sex		
Males	10	7
Females	2	5
Median age (range)	55 (31–74)	63 (22–79)
No. of patients with—		
Extent ("stage") of disease		
Skin-disseminated plaques and tumors ± ulceration	12	12
Lymph nodes-MF and/or dermatopathic changes	8	7
Visceral involvement	2	1
Prior therapy		
Topical agents	3	2
Irradiation (orthovoltage and/or electron-beam)	4	5
Systemic chemotherapy	0	0

TABLE 2.—Results of combination chemotherapy for MF*

SWOG study No. and regimen	Response	No. of patients (%)	Remission duration (wks)		Survival (wks)	
			Median	Range	Median	Range
7204: CHOP or HOP (12 patients)	CR	5 (42)	24	18–68	184	36–269
	PR	7 (58)	18	6–54	52	10+–94
7426: COP + bleomycin (12 patients)	CR	2 (17)	48	18+–48	113+	26+–113+
	PR	9 (75)	53	0+–73+	107	2–109+
	None	1 (8)	—	—	15	—

*See text for details of treatment and definitions of response.

compared to two (17%) of 12 patients treated with COP plus bleomycin ($P = 0.16$). Among the two adriamycin-containing regimens, CHOP appeared to induce CR more often than HOP but the numbers of patients were quite small. For example, of seven patients randomized to receive CHOP, four achieved a CR and three a PR. Only one patient among the five assigned to receive chemotherapy with HOP achieved a CR and four achieved PRs. The overall CR rate was not affected by age, sex, or sites of involvement (skin only versus skin plus lymph node involvement). However, more patients without systemic symptoms appeared to achieve CR than patients who had associated systemic symptoms, although the numbers of patients were too small to reach statistical significance.

The median duration of remission for the seven complete responders was 48 weeks. The response duration was longer for the patients with PR who received COP plus bleomycin. The overall remission duration (CR plus PR) was significantly longer ($P = 0.03$) for patients who received treatment with COP plus bleomycin compared to those who received treatment with one of the adriamycin-containing combinations (fig 1). Remission duration was not affected by age, sex, symptoms, or sites of involvement (skin only versus skin plus lymph node involvement).

The overall survival was not different according to remission-induction treatment as shown in figure 2. The median survival for all 24 patients from the time chemotherapy was initiated was 95 weeks (fig 3). Survival was not affected by age, sex, symptoms, or sites of involvement (skin only versus skin plus lymph node involvement).

The toxicity of the three treatments was similar, but more hematologic toxicity was observed for patients receiving treatment with the adriamycin-containing combinations. One patient developed apparent cardiomyopathy related to adriamycin. Another patient developed potential serious pulmonary toxicity attributable to bleomycin. No serious infections were observed with these treatments and no patients required platelet transfusions.

DISCUSSION

The rarity of MF has hampered systematic studies of combination chemotherapy in this disorder. We were able to identify only 24 patients over a 5-year period with advanced MF who were suitable for trials of combination chemotherapy. The results of our studies, however, demonstrate that combination chemotherapy produces a high objective response rate (95%) with about 30% of patients achieving a complete disappearance of all symptoms and signs of MF. CRs were observed more often with adriamycin-containing combinations (especially CHOP) than with the COP plus bleomycin regimen. Unfortunately, the majority of remissions, either complete or partial, were not durable, and there was no evidence that chemotherapy was curative in advanced MF. The activity of adriamycin and the activity of bleomycin in the treatment of MF have also been noted by Levi et al (8) and Spiegel and Coltman (9), respectively. Surprisingly, overall remission duration was significantly less with the adriamycin-containing combinations than with the COP plus bleomycin regimen (fig 1). At present, we do not have a good explanation for this observation.

In this study, median survival after initiation of chemotherapy for recurrent, advanced MF was nearly 2 years. Survival was similar regardless of remission-induction therapy, although toxicity was less with COP plus bleomycin. Based on these data for advanced MF, we would recommend initial combination chemotherapy with COP plus bleomycin since this was a well-tolerated program. However, additional studies of adriamycin chemotherapy with bleomycin (CHOP plus bleomycin) are clearly warranted in this disease in an effort to improve the effectiveness of systemic chemotherapy for MF.

Much progress has been made in the manage-

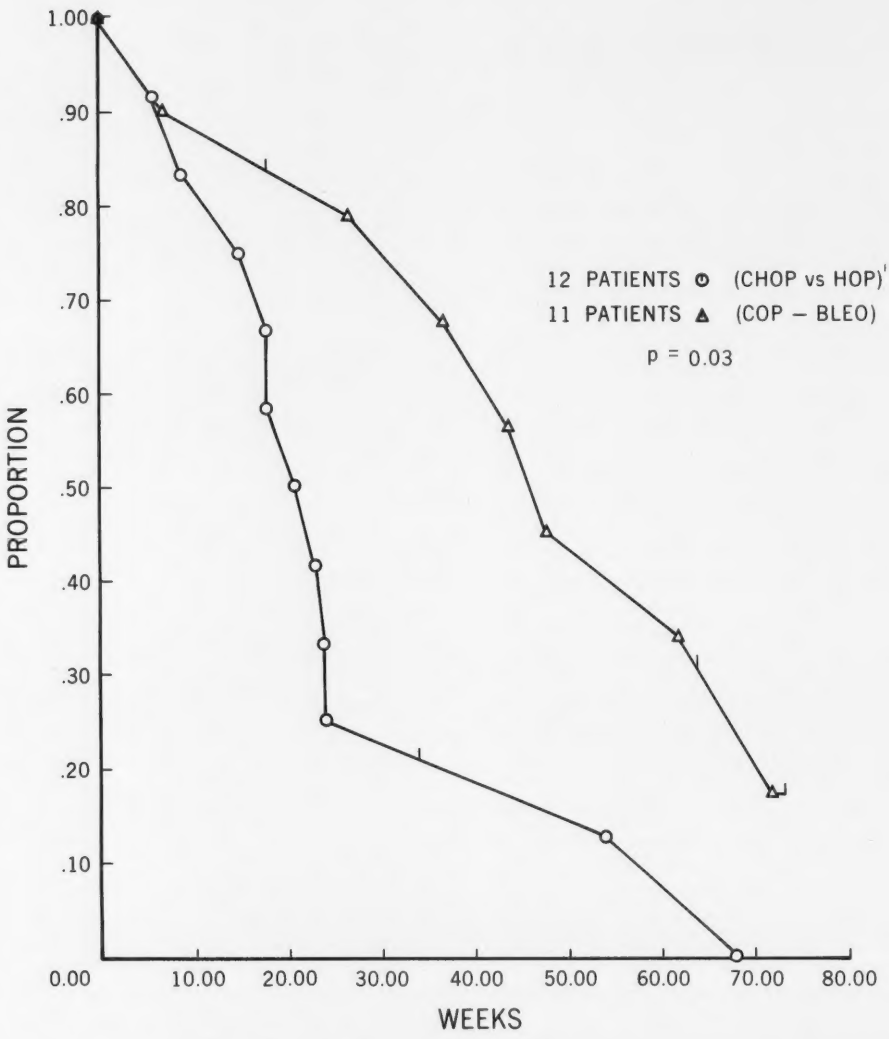

FIGURE 1.—Remission duration according to treatment of MF with adriamycin chemotherapy (CHOP or HOP) vs COP + bleomycin.

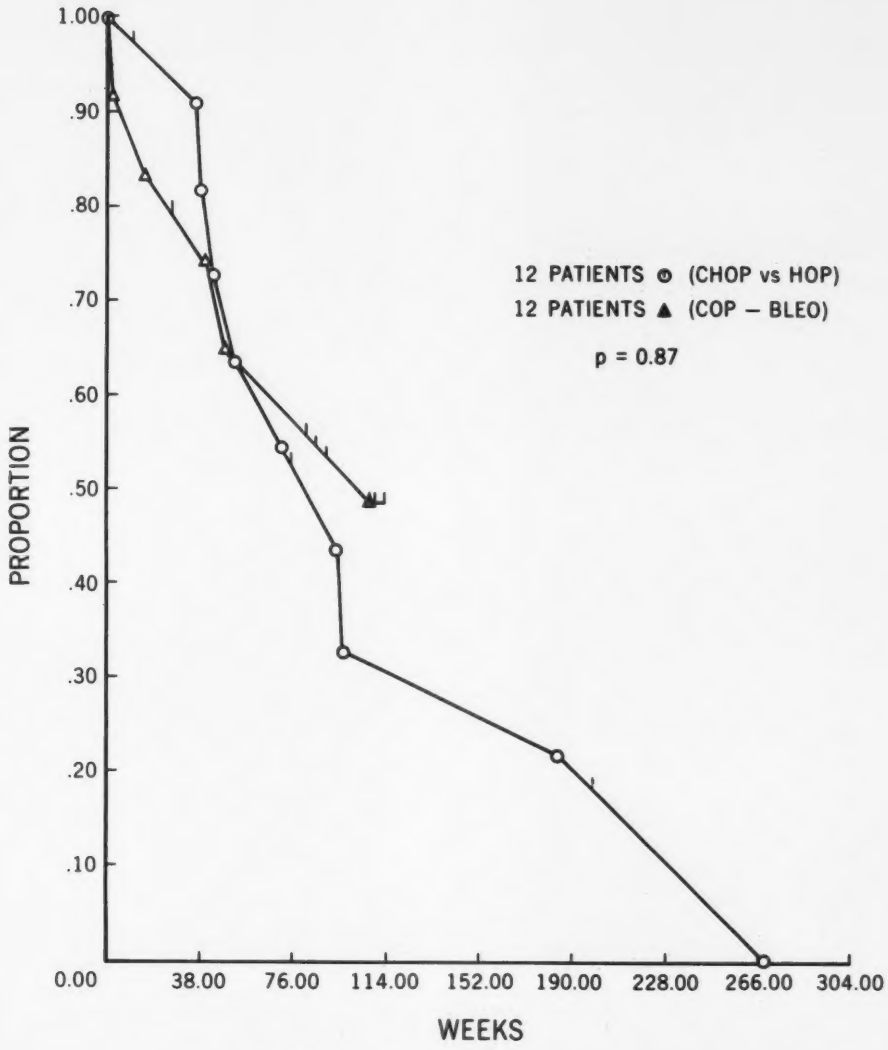

FIGURE 2.—Overall survival according to remission-induction treatment.

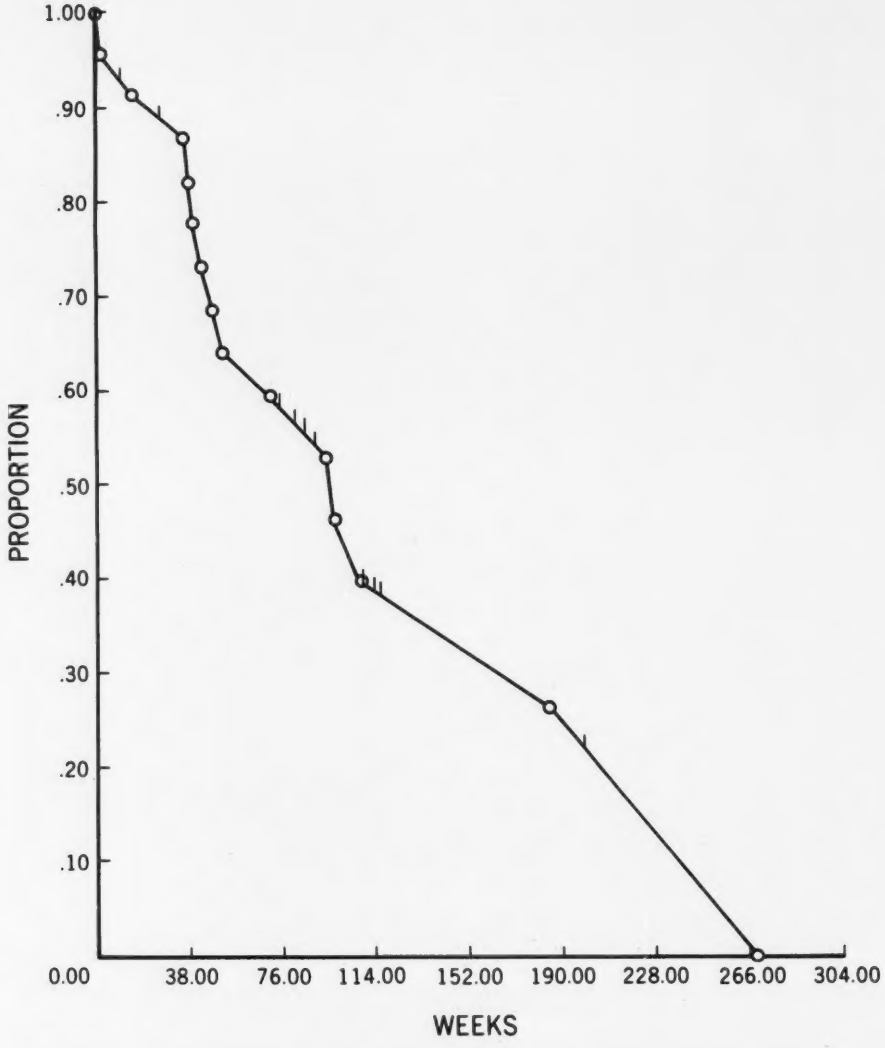

FIGURE 3.—Overall survival for all 24 patients with MF from the time chemotherapy was initiated.

ment of early MF with electron-beam radiotherapy. Indeed, about 40% of patients with limited disease may be cured with radiotherapy (10). The observation that radiotherapy may be curative in some patients coupled with our demonstration of a high response rate to combination chemotherapy provide the basis for trials of adjuvant chemotherapy after potentially curative electron-beam irradiation (11). Such a study has been initiated by the SWOG (study 7622). At the University of Arizona we have treated two patients with six courses of CHOP within 2 months following potentially curative electron-beam therapy. One patient developed new plaques during chemotherapy and the other patient remains free of all evidence of disease 1 year following therapy. We can only conclude that combined modality therapy for early, potentially curable MF is feasible and that such trials must be conducted to improve the end results of treatment.

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Combined Therapy for Patients With Mycosis Fungoides [1]

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SUMMARY

In a comprehensive mycosis fungoides program, 60 patients have been seen with a pathologic diagnosis of this disease. Forty-four patients with advanced disease were referred for radiation therapy. Three treatment techniques were identified in which 14 patients were treated with localized fields using electrons or whole-body electron-beam therapy with doses of < 3000 rads, 21 patients were treated using the Stanford technique with tissue doses of between 3000 and 4000 rads, and nine patients were treated with six cycles of mechlorethamine, vincristine, prednisone, and procarbazine or cyclophosphamide, vincristine, prednisone, and procarbazine following the electron-beam therapy. The actuarial survival rate was 45% at 1 year for the 14 patients with localized electron-beam therapy, whereas the actuarial survival rates were 83% for patients treated with whole-body electron-beam therapy and 100% for patients treated with whole-body electron-beam therapy followed by four-drug chemotherapy. The recurrence-free interval for these three groups correlates with these observations. A central nervous system recurrence has been observed in the combined-therapy group.

[Cancer Treat Rep 63:655–657, 1979]

MATERIALS AND METHODS

From January 1970 to July 1977, 60 patients with histologically proven mycosis fungoides (MF) were evaluated for electron-beam radiation therapy. Following review of the pathology for the diagnosis, 16 patients with superficial disease were excluded and treated with other modalities. The 44 patients treated with electron-beam therapy ranged in age from 21 to 80 years, with a median age of 69 years; no patient was lost to followup. Workup procedures included biopsy of clinically involved lymph nodes, iv pyelogram, inferior vena cavogram, and liver-spleen and gallium scans. In addition, six patients had a Hodgkin's-type staging laparotomy as part of a separate prospective study (1). Table 1 shows the distribution of patients. Fourteen patients showed extracutaneous involvement of lymph nodes, visceral organs (mainly spleen or liver), or Sézary cells in the peripheral blood. Skin lesions were in the tumor stage in 16 patients, eight of whom also had documented extracutaneous involvement. Two patients with erythematous or plaque lesions had concomitant Hodgkin's disease in the lymph nodes. Previous therapy consisted principally of topical corticosteroids, topical mechlorethamine, systemic chemotherapy, immunotherapy, and local radiation therapy. Those patients in the group receiving local treatment included those who were treated with single doses of between 800 and 1000 rads to involved areas and those who received a total skin treatment of < 3000 rads. In the 30 patients receiving whole-body electron-beam therapy, the Stanford technique was used with minor modifications (2). The electron beam was 7.5 MeV generated by the University of Chicago linear accelerator. The primary beam was aimed either above the head or below the feet. Patients were treated in a standing

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TABLE 1.—Summary of patients with MF treated at the University of Chicago

Involvement	No. of patients receiving— Local therapy	Electron beam, full skin	Electron beam + chemotherapy
Cutaneous only	9	14	6
Erythematous and plaque	8	13	0
Tumorous lesions	1	1	6
Extracutaneous	5	7	1
Tumorous lesions	3	5	0
Sézary syndrome	2	2	1
Hodgkin's disease + MF	0	0	2
Totals	14	21	9

position on a platform with both arms raised. Six fields were treated daily to a uniform dose of 200 rads given to the entire skin surface in 2 days. Two thousand rads were delivered to the entire skin in 4 weeks with a 2-week rest period, followed by an additional 2000-rad treatment course. Areas of low dose and shielded areas were treated with single doses of electron-beam therapy given in one fraction at the end of treatment. These areas included the top of the head, top of the shoulders, orbital areas shielded during treatment, perineum, soles of the feet, and, in some female patients, undersurface of the breasts. Between 2 and 4 weeks following the electron-beam therapy, seven patients received mechlorethamine, vincristine, prednisone, and procarbazine chemotherapy and completed six cycles. One patient was given cyclophosphamide instead of mechlorethamine and one patient with Sézary syndrome received chlorambucil, vincristine, and prednisone chemotherapy because of severe bone marrow hypocellularity. These patients did not tolerate a 100% dose of mechlorethamine or procarbazine following the total-skin electron-beam therapy. The planned six cycles of chemotherapy generally took > 6 months because of dose-limiting blood counts.

RESULTS

The 1- and 3-year survival as well as the disease-free interval were calculated using the Kaplan-Meier life-estimation method (3). The actuarial survival and disease-free interval for patients in the three treatment groups are shown in figures 1 and 2 respectively. Complete regression of all skin lesions at the end of treatment was observed in 25 of the patients using the total-skin electron-beam therapy. Five patients with whole-body electron-beam therapy showed a partial response. Only four of the 14 patients using the localized radiation or low-dose electron-beam therapy showed no evidence of disease at the end of treatment. For the localized treatment group, the 1-year survival rate was 45%. The 1-year survival rate was 83% for the total-skin electron-beam technique and 100% for the combined electron-beam therapy and chemotherapy. In those patients receiving combination chemotherapy, recurrences were still seen in the first year; however, the disease-free interval appears to be longer when compared with patients receiving electron-beam therapy alone.

One death has occurred in a patient who received electron-beam therapy followed by adjuvant chemotherapy. This patient had proven MF of the brain and spinal cord as the principal recurrence. The other patients with MF recurring following the six cycles of chemotherapy now have lesions that are quite limited and have been readily managed with topical mechlorethamine or psoralen and ultraviolet light (PUVA).

During the electron-beam therapy, the patients generally had a brisk erythema and some subcutaneous lymphedema. Lymphocyte counts dropped approximately 10% in most of the patients but peripheral leukopenia or thrombocytopenia was not observed. A drop in Sézary cell counts was seen in those patients with Sézary cells in the peripheral blood. Several patients had permanent alopecia, and a decrease in perspiration with resultant heat intol-

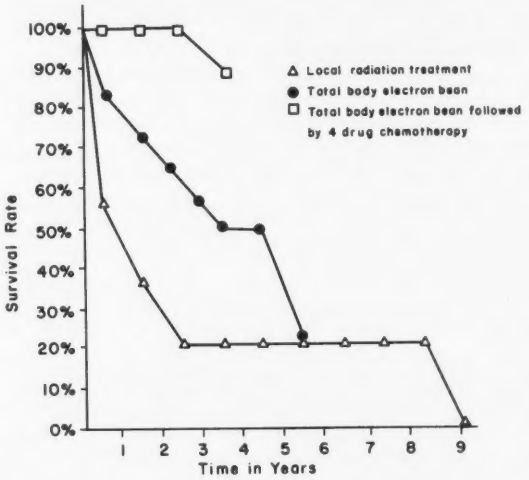

FIGURE 1.—Actuarial survival for patients in the 3 treatment groups.

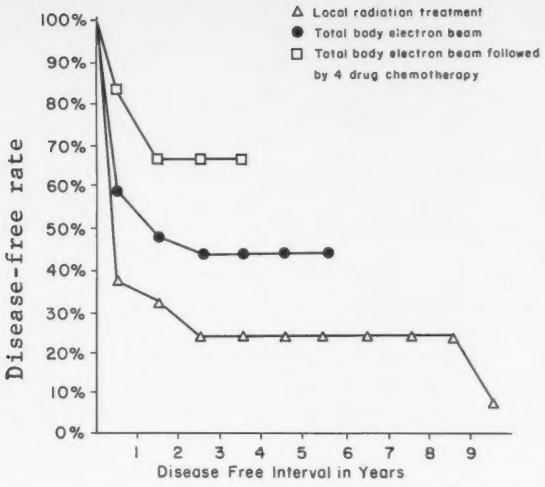

FIGURE 2.—Disease-free interval for patients in the 3 treatment groups.

erance was seen in a majority of patients receiving the whole-body electron-beam therapy.

DISCUSSION

Rosenberg et al (4), at Stanford University, found that radiation therapy followed by combination chemotherapy showed a significant improvement over radiation therapy alone for the treatment of advanced Hodgkin's disease. Rosenberg et al speculated that patients with advanced disease possess occult foci of malignant disease that could not be controlled with radiation alone. They postulated that these occult foci may be adequately treated by combination chemotherapy following adequate cytoreduction of the bulky disease by radiation.

The Stanford group has demonstrated that by complete determination of the extent of Hodgkin's disease through surgical exploration, adequate radiation and chemotherapy can offer significant improvement in survival rates for advanced stages of that disease. In 1975, following this lead, we suggested the need for a more aggressive approach to MF based on our evaluation of surgically staged patients (1). We also postulated that the visceral involvement may be the cause for many recurrences. In 1972, Epstein et al (5) showed that approximately 50% of MF patients died within 2½ years after having cutaneous tumors or palpably enlarged lymph nodes diagnosed. Fuks et al (6) also pointed out the decreased survival in patients with MF with advanced disease.

Our patient, with recurrent disease in the central nervous system following combination radiation and chemotherapy, may represent an interesting observation and one suggesting the ultimate need for sanctuary therapy in selected patients.

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The Kinetics of Sézary Cell Production

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The Sézary syndrome is particularly well-suited for the elucidation of human tumor growth behavior. The cutaneous depot of tumor cells and the circulating pool of Sézary cells are both readily accessible for serial sampling with minimal discomfort to the patient. The presence of multiple kinetic compartments provides for the added dimension of intercompartmental flux analysis.

We have been involved in a collaborative study of the kinetics of the Sézary syndrome. To date, we have analyzed the data from two patients with this disease. Both patients received pulse doses of tritiated thymidine (^{3}H-TdR) iv. Multiple serial samples of blood and skin were then obtained and prepared for radioautographic analysis. These studies will be described elsewhere in detail.[3,4] In this presentation we will simply summarize our conclusions and briefly describe the evidence supporting these conclusions.

Our studies indicate that the skin was *not* the primary site of Sézary cell production in these two patients. This conclusion is based on several lines of evidence.

First, circulating Sézary cells generally do not take up ^{3}H-TdR in vitro (1,2) and do not have the DNA contents of DNA synthesizing cells as determined by flow cytometry.[3] Hence, the ^{3}H-TdR labeling characteristics of circulating Sézary cells must reflect the growth behavior of cells that were proliferating in tissue sites at the time of ^{3}H-TdR pulse exposure and had migrated into the peripheral blood. In both of our patients, the initial labeling index at the > 3-grain/cell threshold for circulating Sézary cells was < 0.01. Maximal circulating Sézary cell labeling intensity was not achieved until 18–24 hours.

In one patient it was readily apparent that the maximal labeling index and the maximal labeling intensity of the cutaneous Sézary cells were not achieved until 18–24 hours after pulse ^{3}H-TdR administration. Since the label is available for incorporation for only 1–2 hours after pulse (3), the increase in labeled Sézary cells in the skin at 18–24 hours must have been due to the influx of circulating cells that had acquired their label initially at some other site of cell proliferation.

Second, since circulating Sézary cells are not proliferating, their mean grain count halving rate must reflect the rate of cell proliferation at the primary site of cell production. In both of our patients the mean grain count halving rate of circulating Sézary cells was much more rapid than the mean grain count halving rate of the cutaneous Sézary cells. Thus, the circulating Sézary cells were derived from a population that was proliferating more rapidly than the cutaneous Sézary cells. Stated another way, the proliferative characteristics of the cutaneous Sézary cells were such that they could *not* have been the source of the circulating Sézary cells.

Our findings are consistent with the kinetic compartment model shown in figure 1. Cells proliferating in a tissue site or sites other than the skin migrate into the blood and later appear in the skin. These cells may proliferate slowly in the skin. Cell loss occurs in the skin compartment, but may occur in other compartments as well.

Where is the primary site of Sézary cell production? The lymph nodes would appear to be the most likely candidates. Kinetic studies are currently in progress which may provide a definitive answer to this question. However, even before the results of such localizing studies are available, one can draw inferences about the size of the primary cell production compartment and the rate of cell production in this compartment from the patterns of acquisition and dilution of label in the peripheral blood, as shown schematically in figures 2 and 3.

If the primary cell production compartment is

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[3]Bunn PA, Edelson R, Ford SS, et al. Patterns of cell proliferation and cell migration in the Sézary syndrome. Manuscript submitted for publication.

[4]Shackney SE. Kinetic compartment analysis in the Sézary syndrome. Manuscript in preparation.

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large relative to the circulating pool, the labeling index of the circulating pool will saturate rapidly (compare figs 2 and 3). If the rate of cell production is high, again, the labeling index of the circulating pool will saturate rapidly (fig 2 [A_1–A_3] and fig 3 [A_1–A_3]), and the mean grain count halving rate of circulating cells will be rapid.

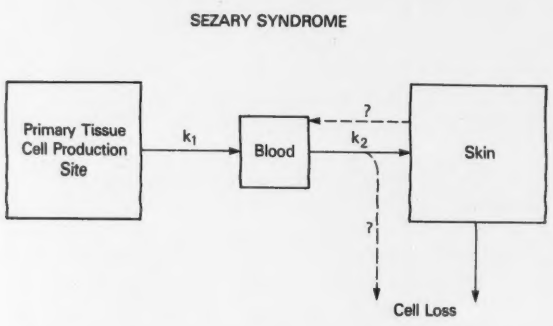

FIGURE 1.—Schematic representation of cell production and cell migration through the various kinetic compartments in the Sézary syndrome. Cells are produced in some tissue other than the skin and migrate into the blood. Circulating cells are then deposited in the skin where they may proliferate slowly. Cell loss may occur at various points.

In practice, one can write differential equations for the three-compartment model shown in figure 1 which, when solved, will yield quantitative estimates of pool sizes and rates of cell production.[5] The results of such an analysis indicate that the primary cell production compartments were quite large in these two patients, ranging from 150 g in one patient to > 1 kg in the other. Compartment turnover times were in the range of 3–5 days in these patients, which is much shorter than one might have expected from what would seem to be a clinically indolent disease. Since disease progression was slow in both patients, such high rates of cell production must have been balanced by comparably high rates of cell loss.

The therapeutic implications of these studies are clear. The Sézary syndrome is a systemic disease. Topical therapy may be useful for tumor "debulking," but systemic therapy will be required for

[5]*See* footnote 4.

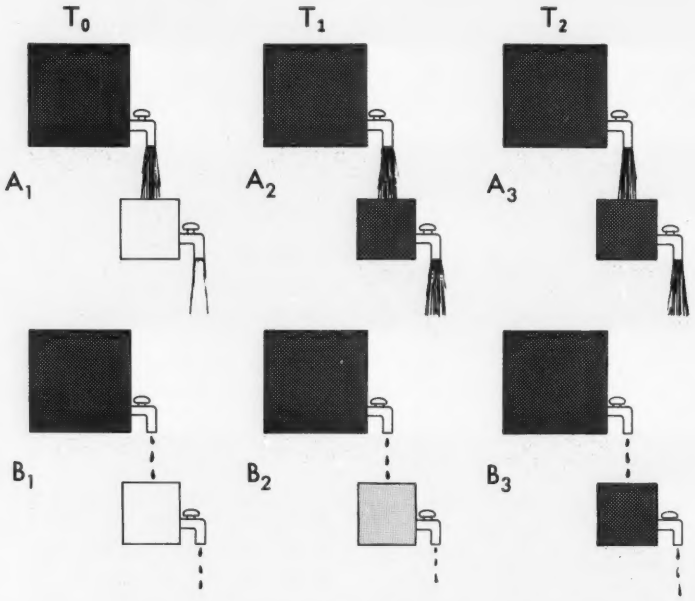

FIGURE 2.—Schematic representation of labeling patterns in circulating Sézary cells in relation to the rate of cell production when the cell production compartment is large in relation to the circulating compartment. A_1–A_3: when the rate of cell production is high, the circulating compartment saturates rapidly. B_1–B_3: when the rate of cell production is low, the circulating compartment saturates slowly, even though the cell production compartment is large.

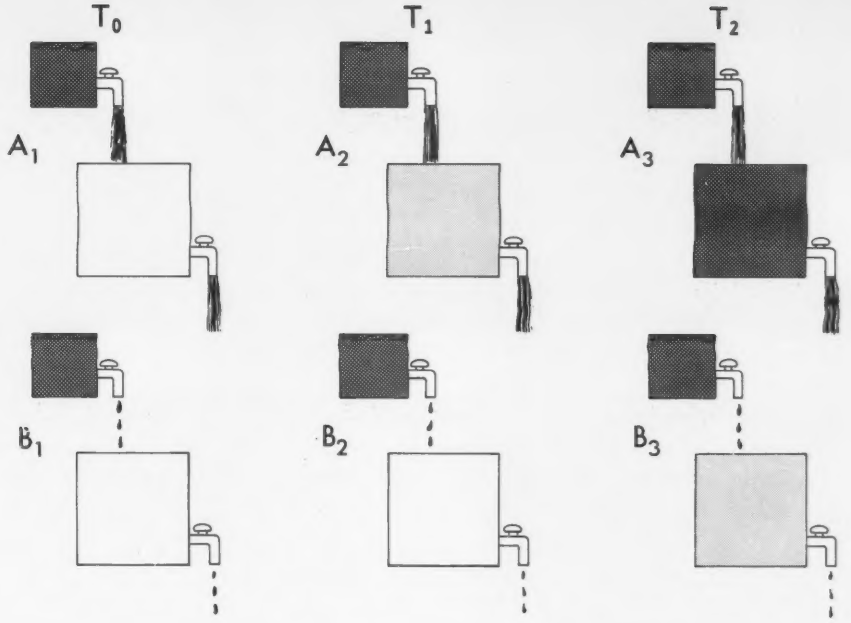

FIGURE 3.—Schematic representation of labeling patterns of circulating cells in relation to cell production when the cell production compartment is small in relation to the circulating compartment. A_1–A_3: even when the rate of cell production is high, the circulating compartment will saturate relatively slowly. B_1–B_3: when the rate of cell production is low, saturation of the circulating cell compartment will take an exceedingly long time.

tumor eradication. In view of the high rates of cell production in this disease, one might expect good responses to chemotherapy, particularly to agents with proliferation rate-dependent lethality. If the lymph nodes can be identified as the primary site of Sézary cell production, then perhaps regional or total-nodal radiotherapy may be worth considering.

We might note that because of the spatial discreteness and accessibility of the slowly proliferating cutaneous Sézary cell compartment, this disease is an exceedingly useful human model for the study of the perturbation effects of chemotherapy. In this respect, the Sézary syndrome provides an ideal clinical setting for the development of principles of therapeutic schedule optimization in man.

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Methoxsalen Photochemotherapy for Mycosis Fungoides

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SUMMARY

Methoxsalen photochemotherapy (PUVA; psoralen plus ultraviolet light) is effective in the treatment of mycosis fungoides (MF). The mechanism of this beneficial effect is unknown but probably involves covalent photo-binding of methoxsalen molecules to pyrimidine bases in DNA at the cellular level and impaired T-cell function or survival at the tissue level. Eleven patients (seven with plaques and four with erythroderma) were referred for PUVA therapy because of poor response to conventional therapy. Seven patients had complete clearing of skin lesions and three improved markedly. All ten of these patients experienced good to excellent control of the disease while receiving maintenance therapy, resulting in a virtual remission lasting for > 2 years in four patients. Of the six patients who discontinued PUVA during the followup period, three died within 1 year and three experienced progression of MF despite conventional therapy. The very promising results in this small patient group should encourage further studies of PUVA for cutaneous T-cell lymphomas.

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In 1974, Parrish et al (1) observed that therapy with methoxsalen, a psoralen derivative, and long-wave ultraviolet light (UVA) was remarkably effective for psoriasis. This type of photochemotherapy (PUVA; psoralen plus UVA) has since been successfully applied to several other apparently unrelated dermatoses, including mycosis fungoides (MF) (2–10). A brief description of PUVA's component parts is pertinent to considering its role in the therapy for MF.

UVA is defined as that portion of the electromagnetic spectrum between 320 and 400 nm. UVA constitutes approximately 5% of the total daily solar irradiance at the earth's surface[2] and is generated in small amounts by conventional fluorescent bulbs. The recent development of a relatively high-intensity UVA light source (12), approximately equal in UVA irradiance to noontime sunshine, permitted systematic exploration of PUVA therapy.

Methoxsalen, or 8-methoxypsoralen, is one of a family of phototoxic furocoumarin compounds. It occurs naturally in numerous plants with a worldwide distribution and can be synthesized in the laboratory. Like virtually all photosensitizing compounds, it is activated by UVA (peak effectiveness between 340 and 360 nm). In the presence of UVA, methoxsalen is known to bind covalently and reversibly to DNA and, to a lesser extent, to RNA and protein (13). Via C4 cyclo-addition it can form both monofunctional and bifunctional adducts to pyrimidine bases (fig 1). These photo-adducts are excised over a period of several hours; the methoxsalen is then metabolized in the liver and excreted in the urine and stool, > 90% of the excretion occurring within 12 hours of oral ingestion.

Central to the concept of photochemotherapy is the fact that these reactions occur only in the presence of appropriate wavelengths of light. In a Caucasian, approximately 60% of UVA energy incident on the skin surface reaches the dermis and < 1% penetrates to subcutaneous fat (fig 2). Hence, PUVA affects cells primarily in the epidermis and papillary dermis. It can have no direct effect on lymph nodes or viscera, although indirect effects are possible.

The mechanism of PUVA's beneficial effect on the

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[2]The other components of solar irradiance are visible light, 50%; heat, 44.8%; and sunburn spectrum UV, 0.2% (11).

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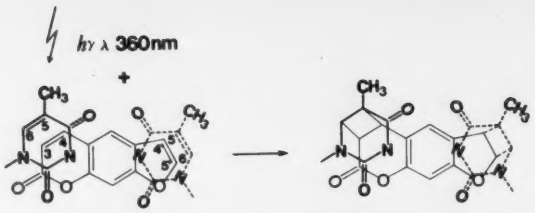

FIGURE 1.—Methoxsalen molecule in proximity to pyrimidine bases of DNA before and after formation of covalent bonds. If bifunctional adduct is formed, DNA strands are cross-linked.

skin lesions of psoriasis, MF, and other diseases is unknown, and indeed may be different for each condition. However, PUVA has been demonstrated to have the following in vivo and in vitro dose-dependent effects: (*a*) delayed erythema (phototoxicity) in normal skin; (*b*) stimulation of epidermal melanocytes, manifested clinically by dark tanning of normal skin and re-pigmentation of vitiliginous skin; (*c*) depression of DNA synthesis and cell division; (*d*) sister-chromatid exchanges; (*e*) carcinogenicity in animal models; (*f*) decreased chemotaxis of polymorphonuclear leukocytes; (*g*) decreased responsiveness of peripheral lymphocytes to standard mitogens; and (*h*) killing of bacteria, viruses, and numerous mammalian cell types, including lymphocytes (13–19). Moreover, thymus-derived (T) lymphocytes are more sensitive than other lymphocyte subpopulations to germicidal light (254 nm) (20); studies of possible differential sensitivity of T lymphocytes to PUVA have not yet been reported. On the basis of the above findings, however, it is reasonable to assume that the clinical and histologic response of MF lesions to PUVA may be due to preferential mitotic inhibition and/or killing of malignant T cells in the skin.

The initial Harvard experience with PUVA therapy for MF has already been reported (2). These nine patients and two additional patients who were treated at the Phototherapy Center, Massachusetts General Hospital, Boston, are the subject of this

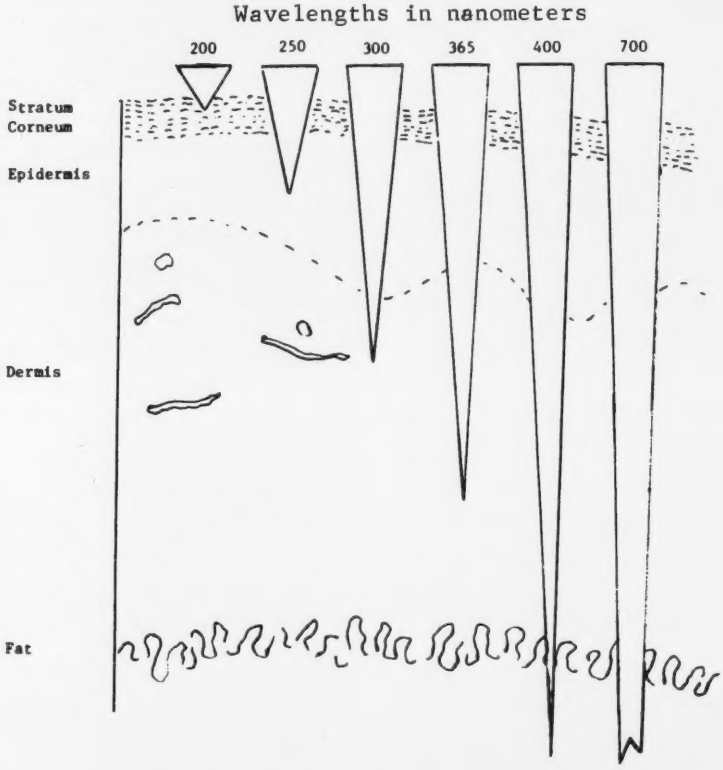

FIGURE 2.—Schematic representation of UVA penetration into skin. Peak effectiveness for methoxsalen binding is 340–360 nm.

paper. Seven had plaque- or tumor-stage MF and four had exfoliative erythroderma or Sézary's syndrome (table 1).

Patients received methoxsalen (approximately 0.6 mg/kg) orally 2 hours prior to UVA exposure in the now standard Sylvania treatment cabinet which provides a continuous spectrum of 320–380 nm with a peak irradiance of 4–6 mW/cm^2 at 365 nm, delivered uniformly over the entire cutaneous surface. The first four patients were treated three or four times weekly; subsequent patients were treated only two or three times weekly since this schedule was found to be equally effective with less risk of painful sunburn reactions. The methoxsalen dose was held constant and the UVA exposures were gradually increased from an average of 3.4 joules/cm^2 (7 minutes) to an average of 16.2 joules/cm^2 (30 minutes) as patients tanned.

All patients had biopsy-proven stage II–IV disease with extensive skin involvement. All were referred for PUVA therapy because of unsatisfactory response to other forms of treatment. Symptoms attributable to MF had been present for an average of 10.7 years, although the period since the first diagnostic biopsy was much less (approximately 3 years).

Skin lesions in seven patients, including three with erythroderma, cleared completely after an average of 5.5 weeks and 16.8 phototherapy sessions. Clinical resolution of lesions was confirmed histologically in at least one site for each patient. Two patients achieved at least 95% clearing of plaques and one erythrodermic patient had marked reduction in redness and scaling. Unfortunately, smears before, during, and after PUVA were not examined methodically in the four patients with Sézary's syndrome. The data available to us are inadequate to conclude that PUVA affected the number or percentage of malignant cells in the circulation. Only one patient, a male with stage IV disease, failed to improve significantly (table 2). Persistent plaques in both partial responders and recurrent lesions in other patients were located in relatively light-shielded areas, such as the scalp and axillae. Lesions in these areas received supplemental treatment as necessary. Once the skin cleared, patients received maintenance PUVA weekly or bimonthly, because in most patients lesions soon reappeared when treatment was discontinued for longer intervals.

Four of the ten responders received PUVA therapy almost continuously for > 2 years, with occasional lapses of < 2 months' duration. All four remained at least 98% free of cutaneous lesions

TABLE 1.—Patients receiving PUVA for MF

Patient No.	Age in yrs/ sex	Type and extent of disease	Duration of symptoms (yrs)	Prior therapy
1	56/F	40% plaque stage	8	Topical intralesional systemic steroids, topical mechlorethamine
2	67/M	70% tumor and plaque stages	28	Topical steroids, topical mechlorethamine, grenz irradiation
3	54/F	40% tumor and plaque stages	6	Topical steroids
4	70/F	70% tumor and plaque stages	18	Topical steroids, topical mechlorethamine, electron-beam irradiation
5	73/M	80% plaque stage	5	Topical steroids, electron-beam irradiation, topical mechlorethamine
6	68/M	Exfoliative erythroderma	7	Mechlorethamine, vincristine (Oncovin), prednisone, and procarbazine (MOPP), topical mechlorethamine, prednisone
7	56/F	95% plaque and tumor stages + lymph nodes	16	Topical steroids
8	68/M	Exfoliative erythroderma	5	Iv and topical mechlorethamine, bleomycin, oral and topical steroids, prednisone, mechlorethamine, vincristine (Oncovin), prednisone, and procarbazine (MOPP)
9	52/M	95% tumor and plaque stages + lymph nodes	6	Topical mechlorethamine, topical and oral steroids, im methotrexate, electron-beam irradiation
10	73/M	Exfoliative erythroderma	13	Topical steroids
11	65/F	Exfoliative erythroderma	10	Electron-beam irradiation, topical mechlorethamine, topical steroids, cyclophosphamide

during this time. Six patients discontinued therapy despite good to excellent control of their disease. Four of these patients discontinued treatment against the advice of their physicians; one patient discontinued treatment because the nearly 2000-mile round trip to our treatment center presented insurmountable problems; and the last patient, whose skin was severely damaged by prior electron-beam irradiation, discontinued treatment because of recurrent painful erythema responses to PUVA. Three of these six patients died within 1 year: one with metastatic squamous cell carcinoma attributed to his prior electron-beam therapy, and two from complications of chemotherapy instituted for control of extensive recurrent MF. In the remaining three patients, the disease progressed despite local electron-beam irradiation, topical mechlorethamine, and systemic chemotherapy over the subsequent 6–18 months.

Side effects of PUVA in most patients consisted of mild nausea, corrected by taking the drug with food; mild generalized pruritus, controlled with emollients and antihistamines; or occasional areas of tender erythema (sunburn). One frail, elderly female (patient 5) had protracted nausea and vomiting on several occasions which was finally stopped by halving the methoxsalen dose; one male, mentioned above, frequently experienced painful phototoxic reactions even at UVA doses believed to be subtherapeutic (1.0 joule/cm^2). No patient had clinical or laboratory evidence of systemic PUVA toxicity, nor did any patient develop signs of extracutaneous lymphoma during the course of PUVA.

Now, 3–5 years after initiating PUVA therapy, only two of these 11 patients remain under our care. One patient continues to do well while receiving maintenance therapy after 4½ years; the other patient relapsed after 3 years despite PUVA therapy and has subsequently required two hospitalizations and adjunctive therapy for ulcerated plaques, although PUVA still aids in control of the lesions. At least three patients have died, as mentioned above, and the remaining six have been lost to followup. This high attrition rate is due, in part, to the five patients referred from outside the Boston area, all of whom found the commuting time intolerable after several months.

PUVA is capable of clearing moderately advanced skin lesions of MF and has provided good to excellent control of the disease in ten of 11 patients for periods ranging from 8 months to 4.5 years. Although, like all therapies for MF at this time, PUVA must be regarded as palliative, it is well-tolerated by most patients and appears to have fewer side effects than other modalities currently advocated for the disease. Further studies are necessary to

TABLE 2.—Response of MF to PUVA

Patient No.	Duration of therapy (mos)	Peak response to therapy	Concomitant therapy
1	27	100% clear	Intralesional steroids to 2 plaques
2	26	98% clear	Intralesional steroids to 2 tumors, local electron-beam irradiation to 8 tumors
3	28	100% clear	
4	18	98% clear	Intralesional steroids to 4 tumors, local electron-beam irradiation to 1 tumor
5	8	100% clear	Local electron-beam irradiation to 2 tumors
6	27	100% clear	
7	16	100% clear, residual alopecia	
8	5	100% clear	Topical steroids for 2 wks
9	2	No change	
10	15	100% clear	Oral prednisone
11	12	Markedly less exfoliation and erythroderma	

define optimal treatment schedules, maximum potential duration of clinical remission, and possible adverse effects of PUVA on the later course of MF.

Nevertheless, our limited experience over the past five years suggests that PUVA deserves serious study as a treatment option for MF.

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Photochemotherapy for Mycosis Fungoides: Long-Term Followup Study

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SUMMARY

A 3-year followup on ten of 12 patients with mycosis fungoides (MF) treated with photochemotherapy (PUVA; psoralens + ultraviolet light) reveals eight patients whose diseases have remained clear while receiving maintenance PUVA. An additional 35 patients with MF have been successfully treated with PUVA. Eight cases of parapsoriasis en plaque have cleared with PUVA. PUVA is indicated in early eczematous and plaque stages of MF. It may be used as adjunctive therapy in tumor-stage MF treated with X-ray therapy or chemotherapy.

[Cancer Treat Rep 63:669–673, 1979]

Mycosis fungoides (MF) is a form of malignant lymphoma that arises in the skin and over many years steadily progresses to plaques and tumors. Autopsy findings often reveal significant visceral involvement at the time of death (1). The premycotic stage is characterized by scaly erythematous patches that clinically resemble nonspecific eczema, psoriasis, or parapsoriasis. When skin lesions reach the plaque and tumor stage, the clinical and histologic diagnosis is more evident.

Therapy for MF is controversial. The course of MF varies from either a chronic long-term process to early death. This variability in the natural course of the disease makes evaluation of therapy difficult. Staging of the disease (2,3) is important in deciding if therapy should be confined to skin lesions or given systemically to eradicate visceral involvement. Topical approaches to therapy include corticosteroids (4), mechlorethamine painting (5–7), and electron-beam irradiation (8).

Methoxsalen has been used for systemic treatment of vitiligo for > 20 years (9). Parrish et al (10) reported successful treatment of psoriasis by combining oral methoxsalen given for systemic effect and a high-intensity longwave (320–390 nm) ultraviolet light (UVA) system. Roenigk and Martin (11) and Lynch et al (12) have confirmed the effectiveness of PUVA (psoralens + UVA) in the treatment of psoriasis and several other diseases. The short-term side effects are minimal and include nausea, pruritus, and erythema. The potential long-term side effects determined from animal toxicity studies (13,14) include skin cancer, cataracts of the eyes, and damaging effects on lymphocytes. These side effects have not yet been confirmed in clinical studies.

The use of PUVA to treat MF was first reported by Gilchrest et al (15) in nine patients with various stages of MF. Roenigk (16) reported 12 cases of plaque, plaque plus tumor, and erythrodermic stages of MF treated successfully with PUVA. Roenigk correlated the histologic clearing of MF lesions with the apparent clinical clearing following PUVA.

This report reviews, with a 3-year followup, the original 12 patients treated by Roenigk (16) at the Cleveland Clinic and expands the experience at Northwestern University with 12 additional patients with MF and three patients with parapsoriasis en plaque (pre-MF). This study also reviews additional reported patients with MF treated with PUVA.

PATIENTS AND METHODS

Twelve patients from the Cleveland Clinic and 12 patients from Northwestern University with clinical cutaneous lesions of MF were studied. The diagnosis was histologically confirmed on repeated skin biopsies. All biopsy specimens were reviewed and confirmed by the pathology panel of the Mycosis Fungoides Cooperative Study Group (17).

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Complete evaluation of all patients included routine laboratory studies, microscopic examination of bone marrow biopsy specimen, roentgenograms of upper and lower gastrointestinal tract, iv pyelogram, liver and brain scans, lymphangiograms, and lymph node biopsies. Only patients with no detectable visceral lesions of MF were entered in the PUVA study.

Ten-milligram capsules of methoxsalen were given according to the method of Parrish et al (10) based on patient body weight as follows: ≤ 50 kg of body weight, 20 mg; 51–65 kg of body weight, 30 mg; 66–80 kg of body weight, 40 mg; and > 80 kg of body weight, 50 mg. Most of the patients were taking 40 mg of methoxsalen. Patients were instructed to take the methoxsalen 2 hours before their scheduled UVA therapy.

Phototherapy units used either of the following two light bulbs: General Electric blacklight (F 72 T12 BL 39 HO) and Sylvania (Parrish et al [10]). Both lamps emit a continuous spectrum of longwave UVA in the range of 320–400 nm, with a peak emission of between 350 and 380 nm. Both lamps are 72 inches long and units were developed with various numbers of bulbs. Sylvania lamps have an internal reflector system and the General Electric lamps use external reflectors.

Initial exposure times of patients to longwave UVA were based on the degree of pigmentation before therapy, the history of ability to tan, and the type of phototherapy units to be used. Exposure times were increased with each treatment depending on patient response, evidence of erythema, and type of phototherapy unit used. The initial UVA dose was between 1.5 and 3 joules/cm^2. Exposure times were increased at each treatment by ≥ 0.5 joule/cm^2 depending on the presence of erythema. UVA-blocking goggles were worn over the eyes during therapy and UVA-blocking sunglasses were worn before and after UVA therapy. PUVA was usually given every 48 hours (3 times a week) during disease clearing.

Once the MF lesions had cleared completely, the patient began receiving a maintenance schedule. The UVA exposure (joules/cm^2) during maintenance was the same as the patient's last treatment during the clearing phase. Maintenance therapy was given once per week for 4 weeks. If the disease remained clear then maintenance was decreased to once every 2, 3, or 4 weeks. All patients were encouraged to continue maintenance therapy with PUVA and not to discontinue therapy as is done in psoriasis.

Photographs, laboratory studies (including special immunologic studies), and skin biopsies were taken before and after therapy with PUVA to evaluate results.

Many of the patients had previously received other therapy for MF including topical corticosteroids, mechlorethamine, superficial X-rays, electron-beam therapy, or chemotherapy. Four patients from the Cleveland Clinic group and 12 patients from the Northwestern University group had received no therapy prior to PUVA.

RESULTS

Cleveland Clinic Group

The specific details of the clearing of disease in these patients have been reported (16). In ten of the 12 patients, long-term followup of ≥ 3 years was obtained (table 1). One patient died (No. 5), but the other nine patients are alive and receiving treatment. Eight of the ten patients are still receiving

TABLE 1.—PUVA in the treatment of MF: 3-yr followup of Cleveland Clinic group

Patient No.	Initial stage of MF	Duration of PUVA (yrs)	Disease status as of Oct 1978	Comment
1	Plaque	3	M_2	Clear
2	Plaque	3½	M_4	Clear
3	Plaque	3	M_3	Clear
4	Plaque + tumor	3	M_1	Clear; deep X-ray to nose
5	Plaque + tumor	1	—	Dead; MF confirmed at autopsy in lung
6	Plaque	4	M_2	Clear; squamous cell carcinoma, arm
7	Erythroderma	3	M_1	Clear
8	Plaque	—	—	Lost to followup
9	Plaque	3	M_2	Clear
10	Plaque + tumor	—		Chemotherapy; lost to followup
11	Plaque	2	—	Tumor lesions; PUVA stopped
12	Plaque + tumor	2	C-2	X-ray to tumor lesion; clear

PUVA therapy and most patients have disease clearance and are receiving maintenance therapy every 1–3 weeks. There has been no progression to tumor stage or systemic involvement with MF. Two patients (Nos. 4 and 12) required additional X-ray therapy for cutaneous tumor lesions. One patient developed a squamous cell carcinoma (No. 6) on the arm which was adequately treated by excision. The patient who died (No. 5) probably had systemic involvement which was undiagnosed at the time PUVA was effective in controlling his cutaneous plaque lesions.

Histologic sections of skin from plaques before and after PUVA confirmed the clinical clearing of lesions in all patients.

Northwestern University Group

The patients treated at Northwestern University have been followed for ≤ 1 year. The clearing phase of these patients (table 2) was similar to that of the Cleveland Clinic group. The one patient who died was referred for treatment with extensive cutaneous lesions and an inadequate systemic workup. An autopsy did reveal systemic MF. Only ten treatments with PUVA had been given and there had been no response to cutaneous lesions.

Five patients with Sézary syndrome and erythroderma have been treated; there were three failures and two responses. Circulating Sézary cells have not been affected by PUVA therapy.

Three patients with parapsoriasis en plaque, considered to be pre-MF, have responded quickly to PUVA.

Histologic sections of skin from plaques before treatment and in those patients whose disease has cleared with PUVA confirm the clinical clearing of lesions.

TABLE 2.—PUVA in the treatment of MF: Northwestern University group

Disease and response	No. of— Good responses	Failures
MF		
Clear	3	
Responding	3	
Dead		1
Sézary syndrome		
Clear	1	
Responding	1	
Dropped from study, flared		3
Plaque parapsoriasis		
Clear	3	
Totals	11	4

TABLE 3.—PUVA in the treatment of MF (all groups)

Disease and response	No. of patients from— Northwestern University	Cleveland Clinic	Mayo Clinic	Total
MF				
Clear	3	9	8	20
Responding	3		2	5
Dropped from study	1	1	2	4
Sézary syndrome				
Clear	1		1	2
Responding	1		1	2
Dropped from study	3			3
Parapsoriasis				
Clear	3		5	8

COMMENTS

Because of the chronic nature of MF and its unpredictable course, treatment must be individualized. Van Scott and Winters (18) have advocated an aggressive approach with topical mechlorethamine. Fuks et al (8) have presented data showing that intensive early electron-beam therapy may be curative. Bluefarb (19) recommended a conservative approach with topical corticosteroids and UVA exposure in mild cases. Chemotherapy following therapeutic measures used for systemic lymphomas has not increased the survival of patients with MF.

PUVA has become a new method of controlling severe generalized psoriasis (10,11). Gilchrest et al (15) first reported the treatment of nine patients in various stages of MF with PUVA using methoxsalen and the Sylvania phototherapy lamp. Roenigk (16) reported 12 patients with MF treated with PUVA and confirmed histologic clearing with at least a 1-year followup. Hodge et al (20) reported six patients with MF whose diseases cleared clinically and histologically with PUVA. Spigel and Muller[2] from the Mayo Clinic reported 14 patients with MF and Sézary syndrome and five patients with parapsoriasis (table 3) treated with PUVA.

This study reports the long-term followup of the original 12 patients treated at the Cleveland Clinic, the early results in 12 new patients from Northwestern University, and the newly reported patients from the Mayo Clinic (table 3). Most patients with eczematous or plaque-stage MF respond with disease clearing from PUVA. In patients with both plaque and tumor lesions the plaque lesions will

[2]Spigel T, and Muller S. Photochemotherapy of mycosis fungoides and parapsoriasis. Presented at the American Medical Association meeting, June 18, 1978.

usually clear but additional X-ray therapy is required for tumor lesions.

Since PUVA is a new form of therapy, long-term cures of MF cannot be claimed. The 3-year followup (table 1) of the Cleveland Clinic group suggests that if MF patients initially respond to PUVA, continued maintenance therapy can keep MF suppressed in the skin without internal progression.

Only one patient in the Cleveland Clinic group died, and he probably had systemic disease before PUVA. Patient 11 had previously received seven electron-beam treatments, had disease clearance on PUVA for 2 years, but later developed cutaneous tumors and was lost to followup. Patients 4 and 12, with both tumor and plaque lesions, have responded to combined PUVA and X-ray therapy for tumor lesions. Two patients from Northwestern University (not included in the 12 patients reported here) had combined PUVA and chemotherapy.

Parapsoriasis en plaque responds quickly to PUVA, and long-term maintenance of these patients might prevent progression to MF.

The failures to respond have been mainly in the erythrodermic (Sézary syndrome) patients. PUVA has also been difficult to administer in erythrodermic psoriatic patients.

The mechanism of action of PUVA in clearing lesions of MF is not completely understood. Methoxsalen is a furocoumarin derivative and a potent photosensitizer with an action spectrum in the longwave UVA range (320–400 nm). Methoxsalen photoreacts with nucleic acids of cellular DNA (21,22). Epstein and Fukuyama (23) have shown that the phototoxic reaction induced by methoxsalen and UVA inhibits semiconservative premitotic DNA synthesis in mammalian epidermis but causes minimal depression of RNA formation. This depression of DNA synthesis is the presumed rationale for its effect on the rapidly proliferating epidermis in psoriasis. The action of PUVA in MF could be due to a direct cytotoxic effect on abnormal lymphocytes in dermis.

Musajo et al (24) demonstrated that irradiation with UVA and methoxsalen inhibited the tumor-transmitting capacity of Ehrlich ascites tumor cells. They indicated that tumor inhibition may be due to inhibition of DNA and RNA synthesis (22). Similar tumor-inhibiting effects have been reported with methoxsalen and UVA in several different tumor systems (25). A similar effect on DNA synthesis and, to a lesser extent, RNA synthesis may be the explanation for the clinical and histologic improvement seen in MF exposure to PUVA.

PUVA therapy has a definite place in the management of MF. It has been proven effective and safe over at least a 3-year followup period. In addition to controlling parapsoriasis en plaque and MF in eczematous and plaque stages, PUVA may be an effective adjunctive therapy used in combination with X-ray therapy and chemotherapy to control tumor-stage and visceral MF.

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Antithymocyte Globulin in the Management of Cutaneous T Cell Lymphoma [1]

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SUMMARY

Four patients with cutaneous T cell lymphoma were treated with iv administered horse antithymocyte globulin. Evidence of a beneficial response was obtained in three of the four patients. Limited sensitivity of neoplastic T cells to complement-mediated lysis in the presence of the antithymocyte globulin was identified, suggesting that other mechanisms may be responsible for the observed clinical responses.

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The application of immunologic methods to the study of human lymphoreticular neoplasms has demonstrated that those processes characterized by widespread skin infiltration are usually T cell malignancies (1–3). Such lymphomas, grouped together as "cutaneous T cell lymphomas" (1,4), include mycosis fungoides and the Sézary syndrome, as well as other clinical histopathologic expressions of T cell neoplasms.

Two of the distinctive features of the abnormal leukocytes in cutaneous T cell lymphoma offer the clinician potentially important therapeutic opportunities. First, in selected patients, the propensity of these leukemic T cells to recirculate between blood and soft tissue compartments makes leukapheresis an effective modality (5–7). Particularly encouraging responses have been noted in those leukemic patients with high blood lymphocyte levels, slow rates of neoplastic cell renewal, and limited bone marrow infiltration. However, at best, leukapheresis markedly reduces tumor load and morbidity and is not a definitive therapy. Second, and of potentially greater importance, the presence of T cell antigens on the membranes of the neoplastic cells may be clinically exploitable through the use of antithymocyte globulin (ATG) (1). Two patients with the Sézary syndrome responded to a short course of ATG (8) with transient improvement. Recently, we reported a dramatic beneficial response to a long course of ATG in a patient with advanced cutaneous T cell lymphoma (9). An additional patient also apparently responded to a short course of ATG prior to dying from an intracerebral hemorrhage (10).

We report here our experience with ATG in the management of four patients with cutaneous T cell lymphoma.

MATERIALS AND METHODS

Patients.—Four patients with widespread skin infiltration by atypical lymphocytes were selected for study (table 1). Three of these patients had the leukemic Sézary syndrome, while one (patient 1) had mycosis fungoides with extracutaneous involvement. The latter patient's course has been previously described in part (9). Prior to administration of ATG, prepared by immunization of horses with human thymocytes as previously described (11),

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TABLE 1.—Characteristics of patients selected for study

Patient No.	Age (yrs)	Sex	Skin	Lymph node	Atypical blood lymphocytes/μl
1	48	F	Tumors and plaques	Effaced	< 50
2	59	F	Erythroderma	—	172,000
3	72	M	Erythroderma	Effaced	2100
4	69	M	Erythroderma	Effaced	23,600

informed consent was obtained in accordance with the Columbia-Presbyterian Medical Center's Human Investigation Committee. A detailed description of the immunologic properties of the neoplastic cells from these patients will be reported separately.

Antithymocyte globulin administration.—ATG was administered iv through peripheral veins in a 3–6-hour continuous infusion. The initial dose of ATG was 250 mg, followed progressively by 500, 750, and, finally, 1000 mg. Intradermal skin tests were performed as a determination of immediate hypersensitivity in patient 1, in whom they were consistently negative. The other patients did not have normal skin suitable for testing.

Cytotoxicity studies.—ATG was diluted to the desired concentration in either RPMI-1640, RPMI-1640 containing 10% normal human serum, or RPMI-1640 containing 10% rabbit serum. Either T cell-enriched fractions of normal mononuclear cells (12) or leukemic lymphocytes from patient 2 (94% of which formed rosettes with neuraminidase-pretreated sheep erythrocytes) were adjusted to 1×10^6/ml in 1 ml of medium containing the desired dilution of ATG. After incubation at 37°C in a water bath for 30 minutes, the suspension was centrifuged for 10 minutes at $800 \times g$. The pellet was resuspended in Hanks' balanced salt solution, and one drop of suspension was mixed with one drop of trypan blue dye on a vaseline coverslip. One hundred randomly encountered cells were scored for viability, as determined by dye exclusion.

RESULTS

Clinical Response to Antithymocyte Globulin

Three of the four patients clinically improved in response to ATG therapy. Patient 1 experienced severe chills and nausea, accompanied by febrile spikes to 104°C, immediately following administration of ATG. In addition, she initially manifested local angioedema in sites of prominent tissue infiltration. This angioedema progressively resolved with continued ATG administration. Although her course has been reported in detail (11), several additional points warrant attention. First, in the third month of treatment (after clinical evidence of disease had disappeared) repeat skin biopsies still demonstrated microscopic involvement of the dermis. Second, after the 14th dose of ATG, pretreatment with 100 mg of prednisolone was given iv and effectively eliminated the febrile spikes, nausea, and chills previously associated with ATG administration. Although a response to the prednisolone may have accompanied use of this agent, the clinical response had already been maximal at a time when ATG was the only therapeutic agent. Third, as shown in figure 1, no adverse effects were noted on granulocyte, platelet, or erythrocyte blood counts compared to the profound effect on circulating T cells, as determined by rosette formation with sheep erythrocytes (fig 2). Fourth, the ATG administration was discontinued after the sixth month because a sclerosing effect on peripheral veins precluded further venous access. Finally, aggressive clinical disease, to be described separately, recurred and ultimately caused the death of the patient secondary to extensive infiltration of all visceral organs examined at autopsy.

Patient 2, a patient with Sézary syndrome, had been followed for 13 months with generalized but moderate erythroderma and a blood lymphocyte count of 21,000–27,000/mm^3, mostly large mononuclear cells with deeply infolded nuclei characteristic of Sézary cells (13). A trial of 60 mg/day of prednisone had failed to affect the blood lymphocytosis but had subjectively decreased the patient's skin discomfort. Progressive tapering to 30 mg of prednisone was accomplished by November 1977, without change in clinical findings. Until January 1978, repeated bone marrow aspirates and biopsies, liver-spleen scans, and peripheral lymph node palpations were within normal limits. On January 18, 1978, the patient was noted to have a blood lymphocyte count of 172,000/μl, with virtually all cells having the above-described atypical morphology. Bone marrow aspiration and biopsy revealed replacement by cells of the lymphoid series, and massive hepatosplenomegaly was evident on physical examination. Combination chemotherapy was begun on January 19, 1978, according to a modified Price-Hill regimen (vincristine, adriamycin, bleomycin, methotrexate

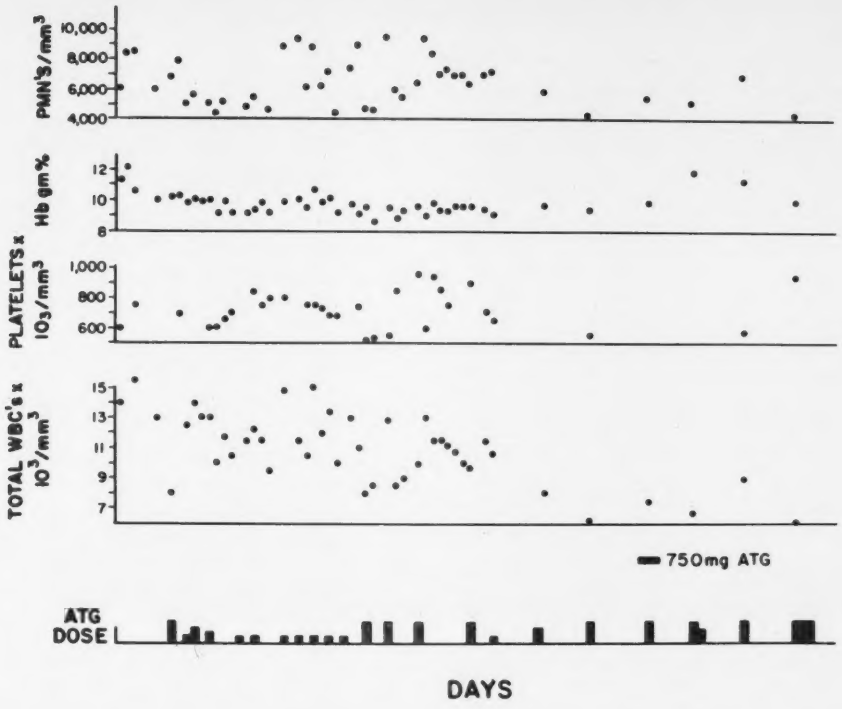

FIGURE 1.—Blood elements during ATG therapy in patient 1. PMN = polymorphonuclear leukocytes; Hb = hemoglobin.

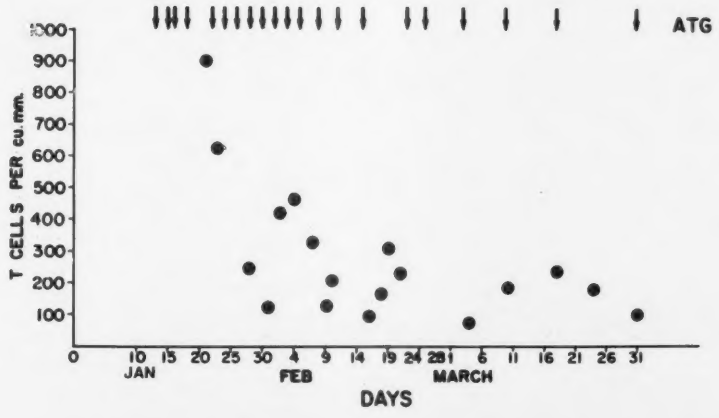

FIGURE 2.—Blood T cell levels during ATG treatment in patient 1. T cells in peripheral blood were quantitated using neuraminidase-pretreated sheep erythrocytes as indicators.

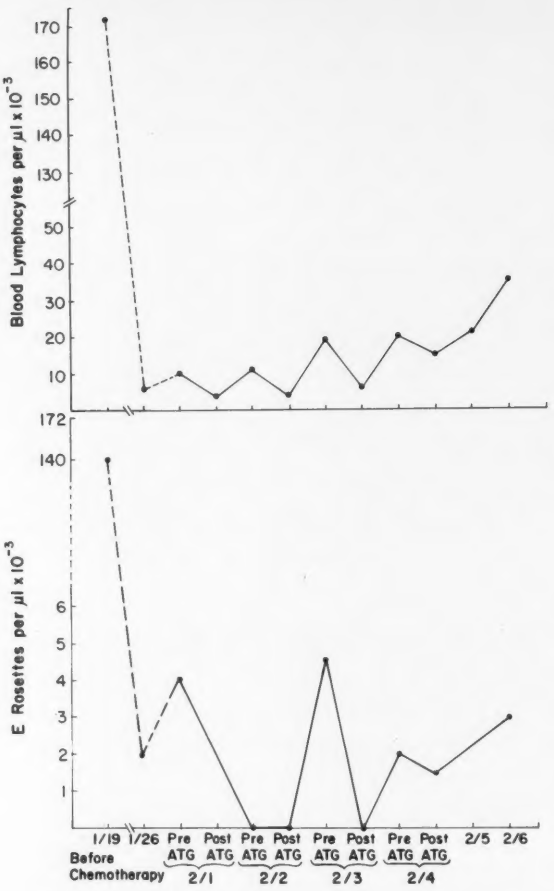

FIGURE 3.—Response to ATG therapy in patient 2 (solid lines). Broken lines describe immediate results following chemotherapy. E = neuraminidase-pretreated sheep erythrocytes.

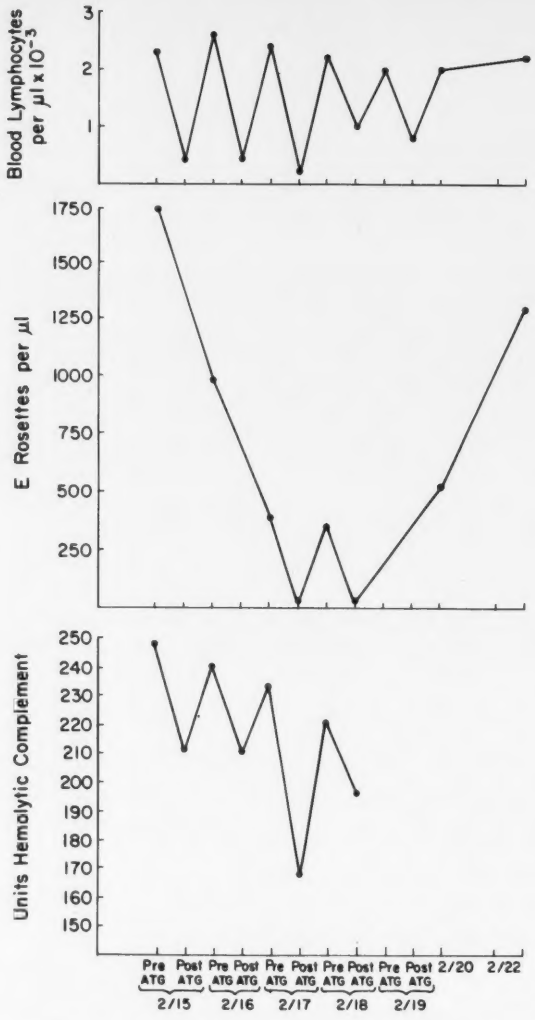

FIGURE 4.—Response to ATG therapy in patient 3. E = neuraminidase-pretreated sheep erythrocytes.

with leucovorin rescue, 5-fluorouracil, and hydrocortisone) (14) with dramatic response, as shown in figure 3. Although this response to chemotherapy will be described in detail separately, it is necessary to briefly describe it here to indicate the setting in which ATG administration occurred. By January 26, 1978, hepatosplenomegaly was no longer evident and the blood lymphocyte count had decreased to 6400/μl. However, the platelet count was only 8000/μl and repeat bone marrow studies revealed continued massive infiltration with few megakaryocytes. ATG administration was begun to attempt to control neoplastic cell renewal while simultaneously not impeding normal bone marrow regeneration. As shown in figure 3, profound reduction of numbers of E-rosette-forming blood lymphocytes transiently followed such treatment. By February 6, 1978, the bone marrow had recovered to the extent that the patient was able to consistently maintain a blood platelet count > 200,000/μl, and a second course of the Price-Hill regimen was administered. She received no further ATG.

Patient 3 received 1 week of daily ATG treatment. Although his erythroderma diminished in severity and significant decreases were noted in blood lymphocyte counts (> 90% of blood lymphocytes had a morphology characteristic of Sézary cells), such improvements were transient and ATG was discontinued. However, as shown in figure 4, a numerical response to ATG was evident. Blood lymphocyte

and E-rosetting cells markedly decreased in response to each ATG administration. In addition, each treatment was associated with a sharp increase in total serum hemolytic complement. The patient did not experience adverse symptomatology related to ATG therapy.

The final patient (No. 4) failed to respond to daily administration of 1000 mg of ATG in any objective way. His cutaneous, peripheral blood, and peripheral lymph node findings did not change. Furthermore, pretreatment with systemic corticosteroids was not required, since he did not experience nausea, chills, or febrile episodes following ATG treatment.

In Vitro Cytotoxicity Determinations

Table 2 summarizes results of complement-mediated lysis of normal and neoplastic lymphocytes. The majority of normal and neoplastic T cells (from patient 2) were lysed in the presence of rabbit complement up to a dilution of 1:1000 ATG. However, human serum appeared to be a less efficient source of complement for these reactions. Significantly, normal T cells were more sensitive to ATG at most dilutions of ATG. Cross-reactivity of normal with abnormal cells was established by the removal of most activity of ATG for normal T cells by absorption with neoplastic T cells.

TABLE 2.—Complement-mediated lysis by ATG

		% lysis	
ATG dilution	Complement source	Leukemic T cells from patient 2	Control T cells (mean ± SD)
1:2	Human	84	87.5 ± 3.5
1:50		41	49.0 ± 5.7
1:100		22	40.5 ± 20.5
1:500		7	24.0 ± 0
1:1000		4	7.5 ± 2.1
No ATG		5	1.7 ± 2.9
1:2 absorbed with neoplastic T cells	Human	—	25.5 ± 12.0
1:2	Rabbit	79	14.5 ± 3.5
1:50		43	80.0 ± 2.8
1:100		50	80.0 ± 12.7
1:500		60	82.5 ± 5.0
1:1000		55	79.0 ± 1.4
No ATG		3	2.0 ± 1.4
1:2	None	8	5.5 ± 5.0
1:50		5	6.0 ± 1.4
1:100		8	8.0 ± 5.7
1:500		4	2.5 ± 0.71
1:1000		5	16.0 ± 1.4
No ATG		10	15.5 ± 0.71

DISCUSSION

Our findings suggest that ATG therapy may be efficacious in the management of patients with extensive cutaneous T cell lymphoma. The mechanism(s) by which ATG administration affects the neoplastic T cells is not clear. Although in vitro results indicate that ATG in the presence of rabbit complement is lytic for both normal and neoplastic T cells, ATG in the presence of human complement is not strongly lytic. Indeed, at dilutions equivalent to those obtainable in vivo, ATG is very poorly lytic for neoplastic T cells in the presence of human complement. It therefore appears that complement-mediated lysis is not the major mechanism by which ATG induces the observed clinical responses. Alternatively, ATG coating of cells may facilitate their removal by the reticuloendothelial system or their destruction by other mononuclear cells. Identification of the mechanism(s) operative in vivo will require further studies.

Liebes et al (15) demonstrated anomalous capping of B cells in chronic lymphocytic leukemia following pretreatment with antilymphocyte serum. Although neoplastic B cells effectively bound the antiserum, aggregation of adherent antibody was deficient. This phenomenon may also occur when the neoplastic T cells of cutaneous T cell lymphoma are exposed to ATG. Normal T cells may more effectively aggregate T cell antigens at one pole of the cell after treatment with ATG and may therefore be more susceptible to lysis than the neoplastic T cells. Alternatively, a deficiency in capping may prevent neoplastic T cells from undergoing antigenic modulation, ie, temporary loss of surface antigen under the influence of specific antibody (16). Decreased antigenic modulation by neoplastic cells would make them more susceptible to lysis by ATG. Clearly, it will be important to establish how effectively the membrane antigens of the abnormal cells of cutaneous T cell lymphoma cap under the influence of ATG.

Conceivably, ATG may have an adverse clinical effect by actually potentiating tumor growth. Iwatsuki et al (17) observed a systemic lymphoblastic response in transplant recipients receiving ATG, and reticulum cell sarcoma has reportedly developed at the site of ATG injection in one additional patient (18). We did not note any acceleration of lymphoma progression in our patients during ATG therapy. However, one patient (No. 1) did develop recurrent aggressive lymphoma after discontinuation of ATG.

All four patients were able to tolerate ATG therapy. Significant reactions included febrile episodes, chills, and nausea immediately following therapy. It

appears that such reactions can be abrogated by pretreatment with corticosteroids. No adverse effects on the numbers of circulating erythrocytes, granulocytes, or platelets were observed. In fact, one patient's chemotherapeutically suppressed bone marrow rapidly regenerated after cessation of chemotherapy and initiation of intensive treatment with ATG. One patient developed angioedema at sites of cutaneous tumors during treatment. Because continued therapy induced resolution of these cutaneous tumors and the angioedema simultaneously subsided, we conclude that the local reaction was secondary to tumor cell destruction. No generalized urticaria, arthralgias, or renal function changes were noted in our series. It is not presently clear whether patients with advanced cutaneous T cell lymphoma are capable of an immune response against the heterologous ATG. Our patients did not produce circulating antibodies to horse immunoglobulin as measured by radioimmunoassay, and no clinical symptoms of serum sickness or anaphylactoid reactions were noted.

The studies described in this paper should encourage further investigation of the effects of ATG on the neoplastic cells of cutaneous T cell lymphoma. It may be possible to produce more specific antibodies which will react preferentially with the abnormal T cells. Furthermore, it may also be possible to conjugate chemotherapeutic agents to ATG and thereby deliver such agents to the neoplastic cells in high concentration. In this context, Beatty et al (19) have demonstrated that an alkylating agent, Trenimon, conjugated to ATG continued to have pharmacologic activity. The application of this technology to the treatment of cutaneous T cell lymphoma merits serious consideration. Finally, because ATG acts at cellular sites and by mechanisms distinct from those of commonly used pharmacologic agents, its beneficial effects may be additive to those of combination chemotherapy.

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A 10-Year Experience With Topical Mechlorethamine for Mycosis Fungoides: Comparison With Patients Treated by Total-Skin Electron-Beam Radiation Therapy [1]

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SUMMARY

A group of 243 patients with mycosis fungoides (MF) received treatment with topical applications of dilute aqueous solutions of mechlorethamine and/or systemic chemotherapy over the past 10 years. The likelihood of a complete and relapse-free remission and survival was found to correlate inversely to the magnitude of disease as denoted by a simple staging system. Although disease-free intervals of > 3 years have occurred thus far in 32 (13%) patients, the permanency of these remissions and the curability of disease remain uncertain because of the variability of disease progression characteristic of MF. Comparison of treatment results with those published on a large group of patients treated with total-skin electron-beam radiation therapy indicates that the chemotherapeutic approach to the treatment of MF is equally effective in promoting survival.

[Cancer Treat Rep 63:681–689, 1979]

In previous papers (1,2), we reported that whole-body topical applications of dilute aqueous solutions of mechlorethamine could be used safely and effectively for long intervals of time to control the cutaneous manifestations of mycosis fungoides (MF) lymphoma. Treatment was particularly effective for patients with early phase of disease with over half of the patients treated maintained in a disease-free status.

In this paper we present our therapeutic results on patients with MF treated with topical mechlorethamine and/or systemic chemotherapy over the past 10 years. Special attention is given to issues concerning duration and permanency of complete remissions (CR) and curability of disease. The influence of treatment on patient survival is assessed by comparing our therapeutic results with those from a large group of patients treated with total-skin electron-beam radiation therapy (3,4).

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Diagnostic Classification and Staging

The age and sex distribution of 243 patients with MF treated during the interval from September 1, 1968, to September 1, 1978, are presented in table 1. The median age of this patient group was 58 years (57 years for males and 58 years for females).

The MF patients were divided into infiltrative and erythrodermic groups according to the predominant clinical features when first evaluated by us. The infiltrative group includes patients with typical premycotic, plaque, or tumorous skin lesions (classic Alibert-Bazin form) and patients with rapidly evolving disease ("tumor d'emblée" form), but excludes patients with other cutaneous lymphomas. The erythrodermic group includes patients with extensive diffuse erythroderma, some with co-existing cutaneous tumefactions, and those otherwise identified as having the Sézary syndrome. All biopsy specimens were reviewed by Dr. Johnson to ensure consistent histopathologic interpretations.

The staging system previously described (2) for infiltrative MF is presented in table 2. For this

TABLE 1.—Age and sex distribution of 243 patients with MF

Age (yrs)	No. of patients in—			
	Infiltrative group		Erythrodermic group	
	Male	Female	Male	Female
10–19	1	0	0	0
20–29	5	0	0	0
30–39	4	8	1	1
40–49	21	11	6	1
50–59	39	19	11	3
60–69	36	22	10	6
70–79	15	8	4	3
80–89	5	1	1	1
Totals	126	69	33	15

presentation, patients with palpable lymphadenopathy whose lymph node biopsy specimens revealed features of dermatopathic lymphadenitis are *not* classified as stage IV. Patients with erythrodermic disease are subclassified according to percentages of easily detectable atypical mononuclear (Sézary) cells on blood smears, an approach that allows for special consideration of patients with the Sézary syndrome.

Treatment Approach

The initial treatment chosen for a given patient varied according to the stage of disease. Topical mechlorethamine was administered initially for the cutaneous manifestations of disease in almost all patients. Those patients with progressive, unresponsive, or otherwise problematic intracutaneous disease usually received additional treatment with single-agent systemic chemotherapy, such as methotrexate or slow-dose mechlorethamine (5). For patients with established extracutaneous disease, single- or multiple-agent systemic chemotherapy was administered at the start of treatment. Thus, topical mechlorethamine was used as primary treatment and systemic drugs were used as adjuvant treatment for early MF and vice versa for late disease.

The use of topical and intralesional mechlorethamine has been described in detail in earlier reports (1,2). Briefly, 10 mg of mechlorethamine powder is dissolved in 1½ to 2 oz of water and the patient is instructed to apply the freshly prepared solution daily over the entire cutaneous surface with relative sparing of the intertriginous zones. The dose and frequency of applications are adjusted according to any encountered irritation and response to therapy. In the event of slowly responding disease, drug applications are increased to two or three times daily governed only by degrees of irritation that may arise. For patients allergic to mechlorethamine, sustained full-dose therapy was usually reestablished following iv desensitization. More recently (2), patients whose disease had virtually cleared following allergic desensitization were

TABLE 2.—Staging classification of infiltrative (classic and "d'emblée) MF*

Stage	Clinical characteristics of skin lesions	Lymph node involvement	Visceral involvement
I	Erythematous patches or minimally infiltrated plaques	0	0
II	Moderately infiltrated papules or plaques, usually associated with erythematous patches	0	0
III	Tumor or nodule formation, usually associated with papules, plaques, or erythematous lesions	0	0
IV	Any of above	+	0
V	Any of above	+	+

*Patients with diffuse extensive erythroderma are classified separately according to the percentages of easily detectable Sézary cells on blood smears.

TABLE 3.—Status of 243 MF patients treated with topical mechlorethamine with or without subsequent additional therapy

Initial classification and stage	No. of patients treated	No. of patients treated with topical mechlorethamine alone	Median time followed (mos)	No. of patients achieving CR (%)	Current status	
					Disease-free (%)	Disease-related deaths (%)
Infiltrative group						
I	79	64	37	63 (80)	42 (53)	1 (1)
II	61	34	36	46 (75)	23 (38)	6 (10)
III	24	3	45	13 (54)	4 (17)	9 (38)
IV	23	0	14	8 (35)	3 (13)	11 (48)
V	8	0	16	3 (38)	1 (13)	6 (75)
Erythrodermic group						
Sézary cells (< 10%)	26	3	52	17 (65)	10 (38)	3 (12)
Sézary cells (> 10%)	22	1	26	5 (23)	1 (5)	12 (55)
All MF patients	243	105	32	155 (64)	84 (35)	48 (20)

treated with topical *nor*-mechlorethamine, an analog of mechlorethamine with relatively less therapeutic efficacy.

Treatment Results

Table 3 summarizes the CR rates and current status of 243 MF patients treated over the past 10 years. Topical mechlorethamine was the only treatment deemed necessary to induce a remission and prevent progression in 98 (70%) of 140 patients with pretumorous infiltrative MF, but was inadequate by itself in more advanced stages of infiltrative disease or in erythrodermic disease. Because our therapeutic objective in patients is to induce and maintain a CR, short-term courses of systemic methotrexate or mechlorethamine were provided to many patients where the response to topical mechlorethamine was adequate, but slow or incomplete. These patients are *not* recorded as being treated with topical mechlorethamine alone, although most of their improvement assuredly was due to topical treatment.

Table 3 indicates that the likelihood of a CR from treatment and the current status depend on the initial magnitude of disease as shown by our staging system. At present, about one third of our patients are free of detectable disease; most of these patients had pretumorous infiltrative disease or erythrodermic MF without large numbers of circulating Sézary cells.

Table 4 contains followup data on 155 MF patients

TABLE 4.—Followup course to date of MF patients who achieved a CR

Initial classification and stage	No. of patients achieving CR	Maximum duration of remission			
		Limited by relapse		Unlimited by relapse	
		No. of patients (%)	Median duration (mos)	No. of patients (%)	Median duration (mos)
Infiltrative group					
I	63	28 (44)	15	35 (56)	28 +
II	46	26 (57)	5	20 (43)	10 +
III	13	11 (85)	12	2 (15)	37 +*
IV	8	6 (75)	4	2 (25)	3 +*
V	3	2 (67)	2*	1 (33)	1 +*
Erythrodermic group					
Sézary cells (< 10%)	17	11 (65)	5	6 (35)	35+
Sézary cells (> 10%)	5	4 (80)	3	1 (20)	42+
All MF patients	155	88 (57)	7	67 (43)	18+

*Nos. too small for significance.

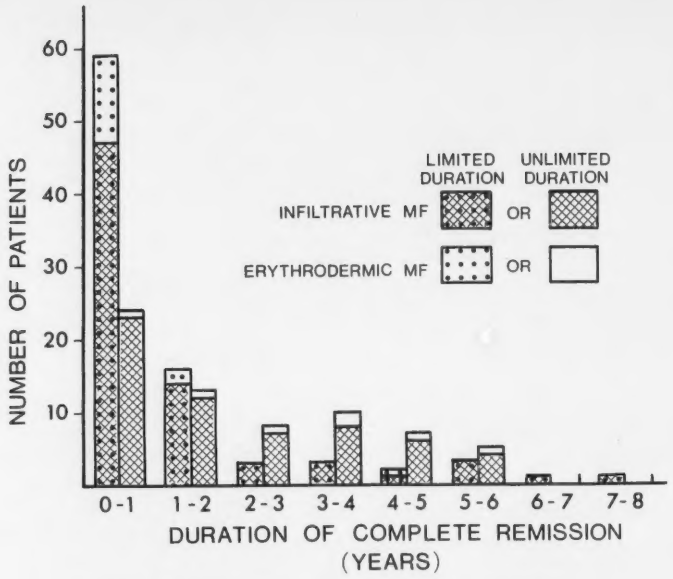

FIGURE 1.—Duration and permanency of CRs in 155 MF patients.

who achieved a CR at some time during treatment. The maximum duration of remission observed for each patient to the present time is recorded as *limited* if any clinical sign of renewed activity of disease was noted after the remission, even in the absence of specific pathologic confirmation, or as *unlimited* if no relapse of disease has occurred to limit the duration of the remission. In 67 (43%) of these 155 MF patients, the maximum duration of remission continues in a sustained, as yet unlimited fashion. The median duration of remission in this group exceeds 18 months. In the remaining 88 (57%) patients, the maximum duration of remission has been limited by a recurrence of disease and has lasted for a median interval of 7 months. These data also indicate that a sustained disease-free remission is considerably more likely when treatment is instituted in early phases of disease.

Figure 1 relates the duration of remission with the observed permanency of CRs in patients with MF. Of 32 patients whose disease-free durations have been > 3 years, five had erythrodermic MF (< 10% Sézary cells, four patients; > 10% Sézary cells, one patient) and 27 had infiltrative MF (stage I, 22 patients; stage II, three patients; stage III, two patients). The sustained remissions in these patients have followed treatment intervals ranging from several weeks, usually interrupted by an allergic reaction to mechlorethamine, to > 4 years. Sixteen patients were directed to discontinue topical mechlorethamine after the CR had exceeded 3 years, and five patients subsequently had a relapse of disease which promptly cleared on resumption of treatment. Thus, a CR of > 3 years' duration does not necessarily guarantee permanency of the remission.

Influence of Treatment on Survival

Survival curves, adjusted to exclude deaths not related to MF, are shown for patients with infiltrative and erythrodermic MF in figures 2 and 3 respectively. These curves were determined by the actuarial life-table method and the numbers at each point denote the number of patients alive at the beginning of each time interval. The z test was used to test the significance of differences in the 5-year survival rate (6).

Within the infiltrative MF group, substantial differences were found among the survival curves of patients at various stages of disease. The 5-year survival rates were 96%, 91%, 68%, 21%, and 0 for patients in stages I–V respectively. The differences in the 5-year survival rates of a given stage from any other stage are statistically significant ($P \leq 0.05$), with the exception of stage I versus II ($P > 0.4$) and stage IV versus V ($P > 0.1$). With stage I and II disease, the difference appears to become significant with further followup. Within the erythrodermic MF group, the 5-year survival rates were 86% and 22% respectively for patients with

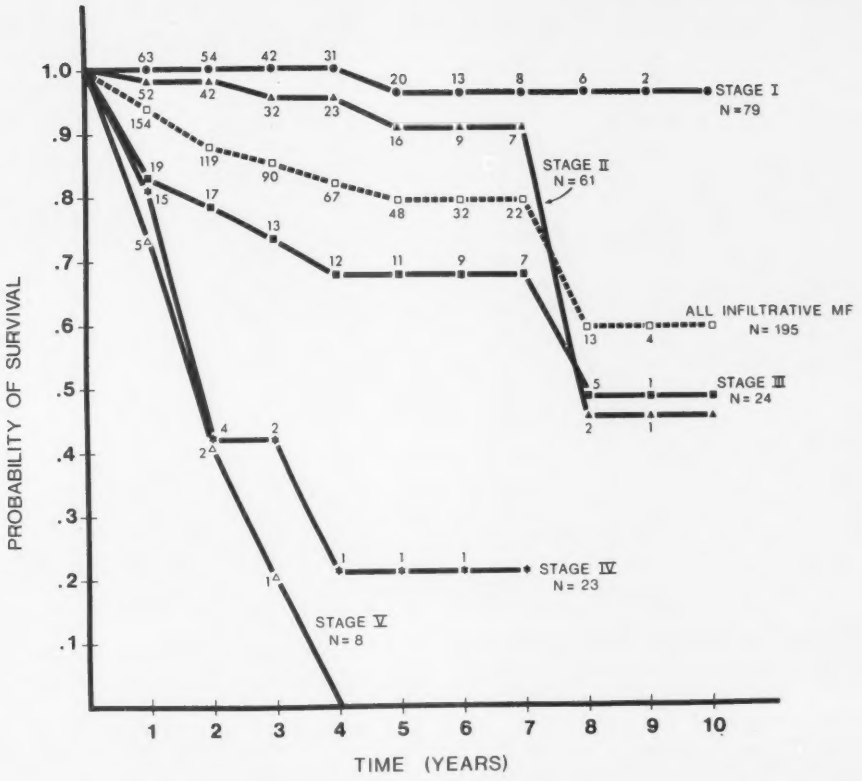

FIGURE 2.—Actuarial survival curves for infiltrative MF according to stage of disease.

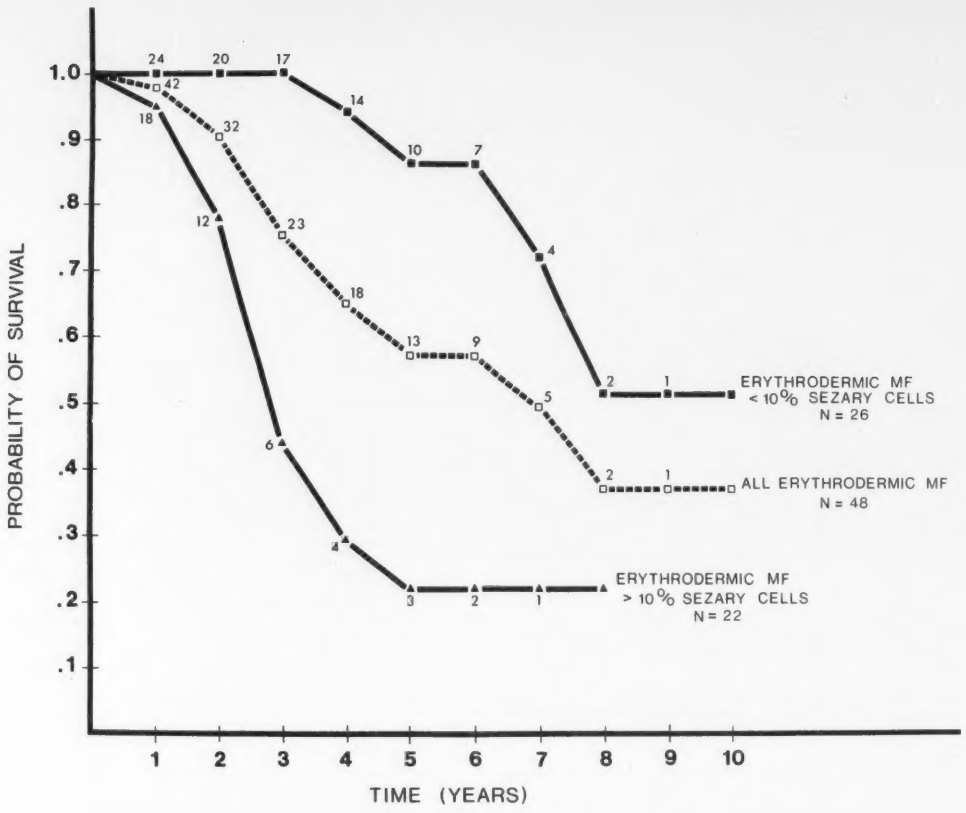

FIGURE 3.—Actuarial survival curves for erythrodermic MF according to percentage of Sézary cells on blood smear.

small and large proportions of circulating Sézary cells, a difference that is highly significant ($P < 0.001$).

Comparison of the survival rates of patients with infiltrative MF to those of patients with erythrodermic disease indicates that the erythrodermic presentation has a relatively unfavorable prognosis. The 5-year survival rate of 79% for infiltrative MF patients is significantly different from the 5-year survival rate of 57% for erythrodermic MF patients ($P < 0.05$). That this difference may somehow be related to the more frequent involvement of extracutaneous sites in the erythrodermic form compared to the infiltrative form is suggested by the more frequent association of circulating Sézary cells within the erythrodermic group. Furthermore, erythrodermic patients with > 10% Sézary cells on initial blood smears have a course quite similar to that of patients with extracutaneous infiltrative MF (stages IV and V).

Comparison With Patients Treated With Total-Skin Electron-Beam Radiation Therapy

The published experience (3,4) on a large group of MF patients treated with total-skin electron-beam radiation at Stanford University, Calif, allows for comparison with our patients treated with topical and/or systemic chemotherapy, provided the data are organized in comparable ways. Table 5 shows clinical data from the Temple and Stanford patients organized as described most recently by Hoppe et al (4). The Stanford classification of "lichenoid MF" is interpreted to indicate patients with diffuse, almost generalized, lichenified disease without marked erythema or variability in the degree of cutaneous infiltration. The Stanford designation of "significant lymphadenopathy" is interpreted to indicate palpable lymph nodes, ≥ 1 cm in size. Comparison of these two patient groups indicates that our patient group has somewhat less extensive degrees of skin involvement

TABLE 5.—Clinical data on 176 and 243 patients treated at Stanford and Temple Universities respectively

	No. of patients in group/total No. of patients			
	Distribution according to skin manifestations		Frequency of significant lymphadenopathy on presentation	
	Stanford	Temple	Stanford	Temple
Eczematous and limited plaque (<50% surface (involvement)	43/176 (24%)	115/243 (47%)	11/43 (26%)	16/115 (14%)
Generalized plaque (>50% surface involvement)	72/176 (41%)	32/243 (13%)	36/72 (50%)	10/32 (31%)
Erythematous	26/176 (15%)	48/243 (20%)	23/26 (88%)	40/48 (83%)
Lichenoid	8/176 (4%)	5/243 (2%)	6/8 (75%)	4/5 (80%)
Tumorous	27/176 (16%)	43/243 (18%)	21/27 (78%)	19/43 (44%)

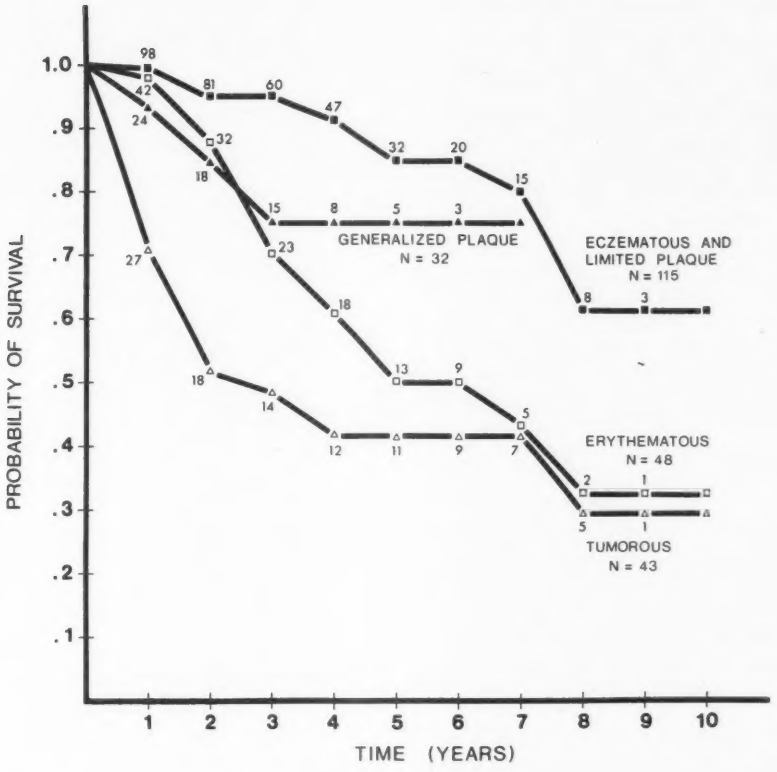

FIGURE 4.—Actuarial survival curves for MF patients classified according to the Stanford system (4).

and is perhaps less likely to develop extracutaneous disease than the Stanford group.

Figure 4 shows the survival curves of our patients classified according to classifications used at Stanford. In order to provide comparable data, these actuarial survival curves reflect deaths from all causes. The 5-year survival rates for limited plaque, generalized plaque, tumorous, and erythematous disease are 85%, 75%, 42%, and 50% respectively for our patients; these results are similar to the 88%, 60%, 11%, and 54% 5-year survival rates reported for comparable patient groups by the Stanford group.

DISCUSSION

Historically, both radiation and mechlorethamine have been recognized as effective therapeutic modalities for MF. Recently, better utilization of each has produced sustained remission to the point that "cure" is now considered possible. Important to both are early and adequate treatment while the disease remains localized to the skin.

With regard to electron-beam radiation therapy, Fuks and Bagshaw (7) were first to present evidence indicating that the posttreatment disease-free intervals justified a more aggressive therapeutic approach than had been previously recommended, particularly in patients with early disease. Most recently (3,4), the therapeutic results of 176 patients treated at Stanford University over the past 18 years have been summarized. The likelihood of a CR and continuous relapse-free survival was found to depend on the dose of radiation therapy administered. With further followup of patients treated with high doses (3000–3600 rads), it is anticipated that the 5-year disease-free survival rate will range between 28% and 43% overall. It is likely that most of these patients are cured of the disease.

With regard to topical chemotherapy, we have demonstrated that long-term complete remissions of > 7 years have followed applications of dilute solutions of mechlorethamine for sustained intervals of time. The ideal treatment schedule, ie, dose, frequency, and duration of treatment, has not been established at this time. Based on data from patients treated with total-skin electron-beam radiation which indicated that a relapse of disease was unlikely after 3 years of disease-free status, we purposely discontinued topical mechlorethamine therapy after 3 years of sustained CRs in 16 patients and have subsequently observed a relapse of disease in five. Therefore, treatment with topical mechlorethamine for longer intervals than previously used may be necessary to achieve total eradication ("cure") of the disease in more patients.

Conversely, long-term remissions have been observed after short intervals of treatment, especially when interrupted by an allergic reaction. The beneficial effect of a delayed hypersensitivity reaction on lesions of MF has been observed before and may represent special influences on the course of disease (2,8,9). However, it is also possible that these observed phenomena reflect the highly variable rate of progression of MF, particularly during its earliest phases (10). Although CRs of long durations occur regularly with treatment with topical mechlorethamine, it is difficult for us to ascertain the "curability" of the disease under these circumstances.

The influence of topical chemotherapy on patient survival is difficult to determine because of the lack of untreated controls and the previously mentioned variability in the natural course of disease. However, the accurate description of the cutaneous manifestations of the patients treated at Stanford does allow for comparison of our treatment results with those achieved by total-skin electron-beam radiation. Convincing evidence has been provided by these investigators to indicate that a substantial benefit on the course of disease can be achieved by high-dose radiation. By comparing comparable patient groups, we found a similar, beneficial influence on subsequent patient survival. However, it is important to note that the Stanford results still reflect a substantial proportion of patients treated with relatively ineffective low-dose therapy. Comparison of our treatment results with those obtained on patients treated with the high-dose electron-beam schedule may be less impressive and must await completion of ongoing prospective studies.

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Electron-Beam Therapy for Mycosis Fungoides: The Stanford University Experience [1]

Richard T. Hoppe, [2,*] Richard S. Cox, [2] Zvi Fuks, [3] Norman M. Price, [2] Malcolm A. Bagshaw, [2] and Eugene M. Farber [2,4]

SUMMARY

The use of high-dose electron-beam therapy for mycosis fungoides at Stanford University is reviewed. Since 1966, 140 patients have been treated in this fashion. Their clinical characteristics including initial extent of disease are reviewed. The results of routine staging studies are examined. Eighty-four percent of the patients achieved an initial complete remission; this was inversely related to the initial extent of skin involvement. The overall survival rate was 46% at 10 years with the major prognostic factor being the initial extent of skin involvement. Other factors which had an influence on the patient's prognosis included the presence of palpable adenopathy, the patient's age, the achieving of an initial complete remission, the initial dose of electron-beam therapy, and the treatment with adjuvant topical mechlorethamine. The development of a rationale for the treatment of patients with all stages of mycosis fungoides based upon these clinical observations is discussed.

[Cancer Treat Rep 63:691–700, 1979]

Total-skin electron-beam therapy for mycosis fungoides (MF) has been used at Stanford University for nearly 2 decades. A total of nearly 250 patients have been treated by this modality. Although our initial approach in the management of this disease was treatment with palliative intent, the clinical response of patients treated with low doses of total-skin electron-beam therapy was impressive (1). Over the years, as it became apparent that patients treated with higher initial doses were more likely to achieve durable remissions, our approach to these patients became more aggressive. We now routinely use high initial doses of irradiation in an effort to achieve long-term control and possible eradication of disease (2). An analysis of the entire Stanford experience in the treatment of MF has been the subject of a recent review (2,3). In this paper, the initial evaluation, treatment, and results of therapy among patients treated in the more aggressive fashion, frequently with curative intent, shall be discussed.

PATIENT CHARACTERISTICS

From October 1, 1966, to December 31, 1977, 141 patients with a biopsy-documented diagnosis of MF were treated with electron-beam therapy at Stanford University. One patient, a 46-year-old man with documented extracutaneous MF involving the lungs, had his skin treated with palliative intent to a dose of only 1000 rads. The remaining 140 patients, all treated with doses of ≥ 2000 rads, form the basis of this study.

Table 1 provides a detailed breakdown of the demographic data. The age range was 20–82 years, with a mean of 55.6 years and a median of 58 years. The age characteristics were similar for patients with each extent of skin involvement.

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The male to female ratio was 1.9:1. The sex ratio was similar among the various groups, except for those with erythematous disease where there were nearly as many females as males.

The duration of symptoms prior to a confirmed diagnosis of MF ranged from several weeks to > 50 years, with a median interval of nearly 5 years. The time from diagnosis to initiation of electron-beam therapy was several weeks to 17 years, with a median of about 2 months.

Staging Evaluation

All patients were evaluated by means of routine physical examination and total-body photographs. There were 73 patients who had lymphography. An evaluation of these lymphograms is the subject of a separate paper (4).

Liver-spleen radionuclide scans were performed in 29 patients. The scans revealed splenomegaly in two patients. A splenectomy was performed on one of these patients, but microscopic examination of the spleen failed to reveal evidence of MF.

A total of 78 patients had percutaneous needle bone marrow biopsy and/or aspirate. Bone marrow involvement was never shown to be present. Percutaneous needle biopsies of the liver were negative in all six patients in whom they were performed.

Five patients had staging laparotomy as part of a prospective trial to study the natural history of MF. Extracutaneous MF was demonstrated in only one patient, and in this single instance it had been apparent clinically as well.

Extent of Disease

Table 1 shows the distribution of patients by their initial extent of skin involvement. Nearly half of the patients were in the generalized plaque phase (> 25% of body surface area involved) (5). There were nearly equal numbers of patients with limited plaque (< 25% of body surface area involved), tumorous, and erythematous disease. The lichenoid variant was very rare.

TABLE 1.—Extent of skin involvement, age, and sex ratio of 140 patients with MF

Extent of skin involvement	No. of patients	Age range in yrs (mean)	Male:female ratio
Limited plaque	25 (18%)	33–71 (54)	17:8
Generalized plaque	67 (48%)	22–75 (54)	46:21
Erythematous	21 (15%)	31–79 (60)	11:10
Lichenoid	2 (1%)	31–62 (47)	2:0
Tumorous	25 (18%)	20–82 (57)	16:9
Totals	140 (100%)	20–82 (55.6)	92:48 (1.9:1)

TABLE 2.—Distribution by stage of 140 patients with MF

Stage	No. of patients	%
IA	23	16
IB	66	47
II	42	30
III and IV	9	7
Totals	140	100

Patients were assigned to a stage based on the extent of skin involvement and the presence of extracutaneous disease as follows: *stage I*—MF limited to the skin with no tumors, ulcers, significant adenopathy, or visceral involvement (clinical or pathologic); *stage IA*—eczematous or limited plaque disease with involvement of < 25% of the total-skin surface; *stage IB*—involvement of > 25% of the total-skin surface (includes generalized plaque, lichenoid, and generalized erythroderma variants); *stage II*—presence of skin tumors or biopsy-proven dermatopathic lymphadenopathy with no extracutaneous involvement; *stage III*—MF involving the skin with biopsy-proven involvement of the lymph nodes or spleen and no other visceral involvement; and *stage IV*—cutaneous and extracutaneous MF with documented visceral involvement. Table 2 shows the distribution of patients by stage. The most common presentation was with generalized skin involvement in the absence of skin tumors, dermatopathic lymphadenitis, or extracutaneous MF (stage IB). Only nine patients (7%) had documented MF involving the lymph nodes or viscera (stages III and IV). More than half of the patients (58%) had palpable lymphadenopathy at the time of presentation (table 3). The likelihood of palpable lymphadenopathy increased from only 20% among patients with limited plaque disease to 84% among those with tumorous lesions.

We currently perform routine lymph node biopsies in all patients who have palpable adenopathy. Most of the patients in this series had selective lymph node biopsy because of clinically worrisome lymphadenopathy. Table 3 shows the results of node biopsies in 47 patients. The most common histologic interpretation was dermatopathic lymphadenitis. Only nine patients had lymph node biopsies which showed changes consistent with MF. The likelihood of initial lymph node biopsies being positive for MF when the disease on the skin consisted of plaques alone was extremely low (one of 18 patients, 6%). The likelihood of lymph node involvement in pa-

TABLE 3.—Lymph node evaluation in 140 patients with MF

Extent of skin involvement	Total No. of patients	No. of patients with—		Lymph node biopsy results (No. of patients in category indicated/No. with biopsy)		
		Nonpalpable lymph nodes	Palpable lymph nodes	Negative or reactive	Dermatopathic lymphadenitis	MF
Limited plaque	25	20 (80%)	5 (20%)	1/3	2/3	
Generalized plaque	67	31 (46%)	36 (54%)	3/15	11/15	1/15
Erythematous	21	4 (19%)	17 (81%)	2/13	8/13	3/13
Lichenoid	2	0	2	—	—	1/1
Tumorous	25	4 (16%)	21 (84%)	6/15	5/15	4/15
Totals	140	59 (42%)	81 (58%)	12/47	26/47	9/47

tients with more advanced skin disease was substantially higher (eight of 29 patients, 28%). The actual incidence of lymph node involvement by MF would probably be less if all of the patients in this series had received routine lymph node biopsy.

THERAPY

All patients received a course of total-skin electron-beam therapy with doses ranging from 2000 to 4000 rads over 61–260 days. The techniques of treatment and complications of therapy have been discussed in detail elsewhere (6). Patients were evaluated initially and followed subsequently at the conjoint Mycosis Fungoides Clinic at Stanford University. The range of followup was 0.3–11 years, with a median duration of > 3 years. Only six patients, five of whom had been followed for at least 4 years, were lost to followup.

Adjuvant therapy with topical mechlorethamine was initiated in selected patients within 3 months after the completion of electron-beam therapy. Patients usually were selected for adjuvant treatment because of adverse prognostic signs such as dermatopathic lymphadenitis or tumorous involvement of the skin (7). The daily application of topical mechlorethamine was performed in a manner similar to that originally reported by Van Scott and Kalmanson (8). Patients who became hypersensitive to the topical mustard generally were desensitized successfully by means of a gradual dose-escalation schedule (9).

RESULTS

An analysis of the data was performed on a PDP-11/50 computer (Digital Equipment Corp). Actuarial survival and freedom-from-relapse curves were calculated by the technique of Kaplan and Meier (10). The generalized Wilcoxon test developed by Gehan

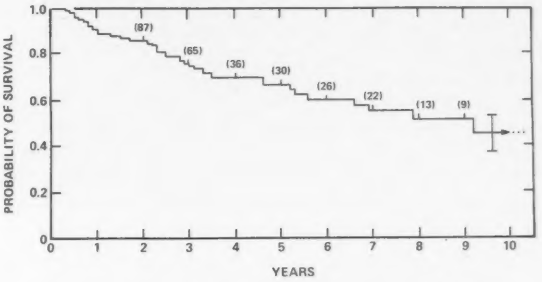

FIGURE 1.—Actuarial survival of 140 patients with MF.

(11) was used to assess the significance of differences between the various groups. Survival was calculated from the date of initiation of electron-beam therapy and freedom from relapse was calculated from the date of completion of treatment

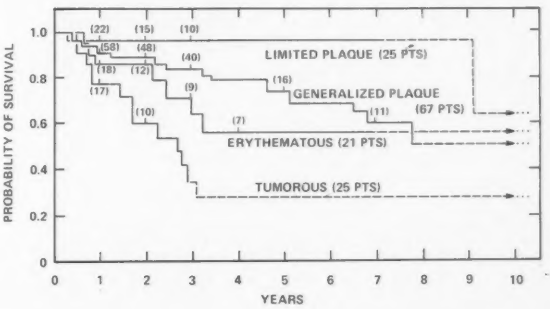

FIGURE 2.—Actuarial survival as a function of extent of skin involvement in 140 patients with MF. *P* values include limited plaque vs tumorous, < 0.002; limited plaque vs erythematous, < 0.08; limited plaque vs generalized plaque, < 0.18; generalized plaque vs tumorous, < 0.002; and erythematous vs tumorous, < 0.14. The broken lines indicate that < 5 patients are at risk.

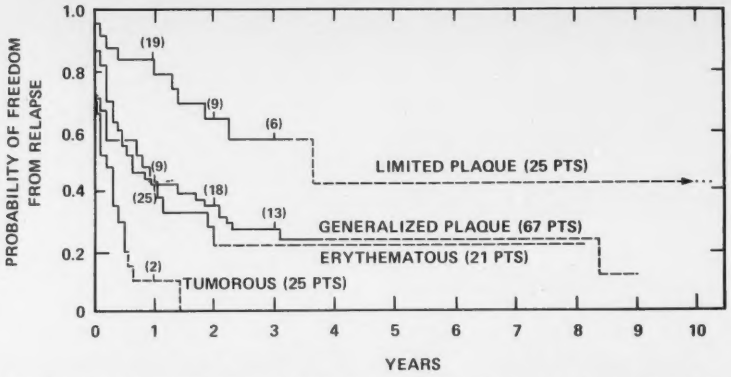

FIGURE 3.—Freedom from relapse as a function of extent of skin involvement in 140 patients with MF. The broken lines indicate that < 5 patients are at risk. These curves start at < 1.0 because not all patients achieved an initial CR. *P* values include limited plaque vs generalized plaque, < 0.005; limited plaque vs erythematous, < 0.005; limited plaque vs tumorous, < 0.0001; generalized plaque vs tumorous, < 0.0001; and erythematous vs tumorous, < 0.12.

Initial Complete Remission (CR)

An initial CR was observed in 84% of the patients (118 of 140 patients) (table 4). The likelihood of achieving an initial CR was inversely related to the extent of skin involvement and ranged from 96% in the limited plaque group to only 72% in patients with skin tumors.

Overall Survival

Figure 1 shows the overall survival of these 140 patients. The median survival is > 9 years and the survival rate is 46% at 10 years.

Effect of Extent of Skin Involvement

Figures 2 and 3 display the survival and freedom-from-relapse curves of patients classified by the extent of skin involvement. Patients with limited plaque disease had the best survival rate (96% at 9 years) and also enjoyed the best freedom-from-relapse rate (42% at 10 years). Patients with tumorous involvement of the skin had the worst prognosis with a 10-year survival rate of only 28% and a median survival time of only 2.7 years. No patient with skin tumors remained disease-free for > 1.5 years. The prognosis of patients with generalized plaque or erythematous forms of skin involvement was intermediate between those who had limited plaque or tumorous disease. At 10 years, the median survival of the generalized plaque and erythematous groups has not yet been reached.

Most of the relapses occurred within the first year after completion of therapy and were very rare after > 3 years. The median disease-free interval was > 3 years for patients with limited plaque disease, approximately 1 year for patients with

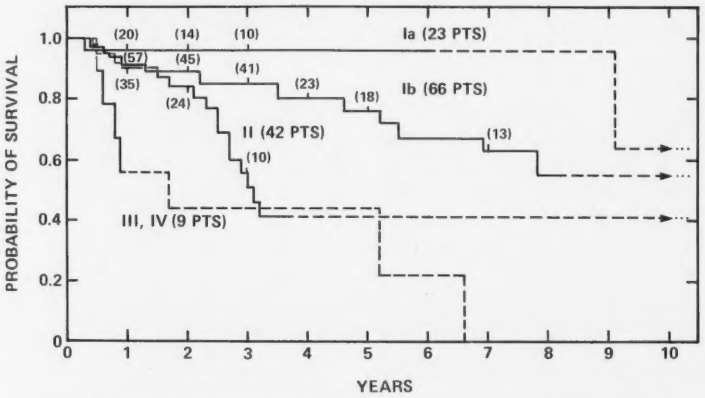

FIGURE 4.—Actuarial survival as a function of stage in 140 patients with MF. The broken lines indicate that < 5 patients are at risk.

TABLE 4.—Probability of achieving a CR as a function of the initial extent of skin involvement in 140 patients with MF

Extent of skin involvement	No. of patients with CR/total No. of patients	% CR
Limited plaque	24/25	96
Generalized plaque	60/67	87
Erythematous	15/21	71
Lichenoid	1/2	50
Tumorous	18/25	72
Tot.	118/140	84

either generalized plaque or erythematous disease, and < 6 months for patients with tumorous involvement of the skin.

Influence of Stage

A patient's initial stage also has a bearing on prognosis (figs 4 and 5). There was only one death in the first 9 years of followup among 23 patients who had limited plaque disease without dermatopathic lymphadenitis (stage IA). The survival rate was only 55% at 9 years for patients who had generalized skin involvement without dermatopathic lymphadenitis (stage IB). The presence of skin tumors or dermatopathic lymphadenitis (stage II) had an even more adverse effect on prognosis, with a median survival time in this group of only 3.1 years. The median survival time of patients with extracutaneous disease is only 1.7 years, and with a single exception, all of these patients have died. While the long-term survival rate is 41% for patients with stage II disease, very few of these patients remain disease-free. Figure 5 shows that the freedom from relapse in these patients with skin tumors or dermatopathic lymphadenitis is virtually identical to that in patients who have known extracutaneous involvement (stages III and IV).

Prognostic Factors in the Generalized Plaque Group

In this series the most common extent of skin involvement was the generalized plaque phase. This group is homogeneous with regard to the extent of skin involvement and large enough (67 patients) to permit the evaluation of several possible prognostic factors.

The presence of palpable adenopathy has been reported to have an adverse effect on the prognosis of patients with MF (12). Figure 6 shows the influence of this clinical observation among a group of patients with similar stages (generalized plaque) who are similarly treated (high-dose). Although the survival of these patients is excellent in either case, the freedom from relapse is much worse among patients with palpable lymph nodes (13% versus 48% after 3 years).

Another factor which appears to affect prognosis is age. Its influence is shown in figure 7. Patients in the youngest third of the population (<50 years) have the best prognosis ($P < 0.006$; $P < 0.003$). Patients in the middle and oldest thirds of the population appear to have rather similar survival ($P < 0.36$). A similar analysis for freedom from relapse (not shown) shows the same effect of age on prognosis.

The duration of a patient's symptoms prior to diagnosis or initiation of electron-beam therapy did not have an effect on prognosis. While patients with abnormally low lymphocyte counts did more poorly than patients with normal lymphocyte counts, this difference became less apparent when patients were

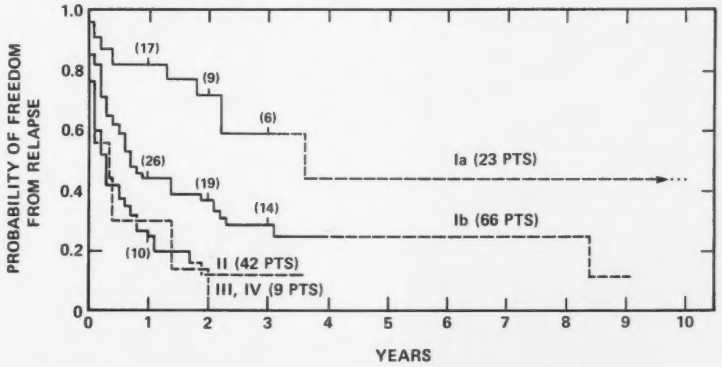

FIGURE 5.—Freedom from relapse as a function of stage in 140 patients with MF. The broken lines indicate that < 5 patients are at risk.

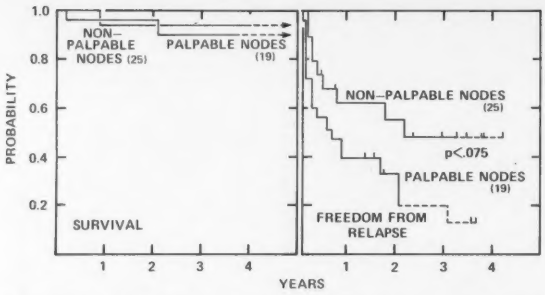

FIGURE 6.—Effects of palpable adenopathy on survival and freedom from relapse among 44 patients with generalized plaque MF who were treated with high initial doses of electron-beam therapy. The broken lines indicate that < 5 patients are at risk.

grouped by the initial extent of skin involvement and did not reach statistical significance.

In addition to those risk factors which reflect either the extent of disease or the general prognosis of a patient, there are several variables in a patient's treatment which also appear to influence his prognosis. Figure 8 shows that the single most important factor of this type is initial remission status. The survival rate is 63% at 10 years among the 60 patients who achieved an initial CR. In contrast, all seven patients who failed to achieve CR have died after 0.4–6.5 years. This difference is statistically highly significant ($P < 0.0001$).

The initial dose of electron-beam therapy has been shown to have an effect on survival when patients treated with doses of 800–2499 rads are compared to those treated with doses of ≥ 2500 rads (6). Even within the high-dose restrictions placed upon the patients in this series, the initial dose of electron-beam therapy has an important effect on prognosis. Figure 9 shows that patients treated with doses of ≥ 3000 rads had a significantly better survival than those treated with doses of < 3000 rads ($P < 0.006$). A similar trend was observed for freedom from relapse (not shown), but the difference was not quite statistically significant ($P < 0.06$). These differences persisted even when the results were adjusted for age differences in the population.

Figure 10 shows the effect of adjuvant topical mechlorethamine therapy. All of the patients who received topical mechlorethamine also received initial doses of electron-beam therapy of ≥ 3000 rads. Although there is a hint of improved survival in the adjuvant group, this is not statistically different from patients treated with high doses of radiation alone. The differences in the freedom-from-relapse figures were similar and suggested that there might be a delay in relapse as a result of the adjuvant therapy. The benefit derived from adjuvant therapy persisted even when the populations were adjusted for age differences.

DISCUSSION

MF has a long natural history. It often progresses slowly, even without specific therapy. This lengthy course is frequently complicated by difficulty in establishing the diagnosis. Patients with a clinical history consistent with MF may undergo repeated skin biopsies over a period of many years before the changes diagnostic of MF become apparent. Although the cutaneous lesions of MF are exquisitely sensitive to local modalities such as topical mechlorethamine (8) and orthovoltage X-rays (13), the disease usually progresses and often causes death due to skin infection and sepsis or extracutaneous involvement by tumor.

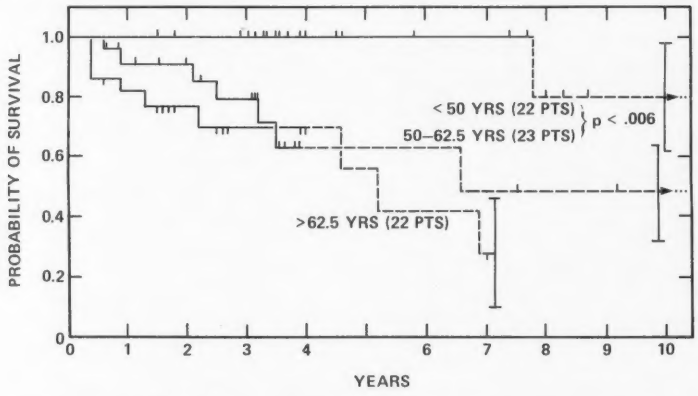

FIGURE 7.—Effects of age on survival of 67 patients with generalized plaque MF. The broken lines indicate that < 5 patients are at risk.

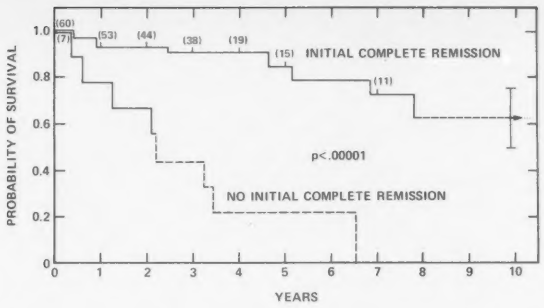

FIGURE 8.—Effects of initial remission status on survival of 67 patients with generalized plaque MF. The broken lines indicate that < 5 patients are at risk.

An evaluation of the results of treatment in MF is difficult. No series, including our own, has included a concurrent randomized group of patients who received no therapy at all. And yet, the claim has been made that no specific therapy is indicated for the early stages of this disease (14). Our own historical perspective suggests an improved remission rate and response duration when patients are treated with high doses of electron-beam therapy rather than with low, palliative doses (2,3,6). When low and high doses of radiation were compared we found that both survival and freedom from relapse were better among patients treated with the higher doses. This observation remains an important factor even among the patients in this series, all of whom received doses of ≥ 2000 rads. Patients treated with doses of ≥ 3000 rads fared significantly better than those who were treated with 2000–2999 rads (fig 9).

Other factors appear to be important as well. Among the patients with generalized plaque disease, the younger patients did better than the older patients (fig 7). The addition of topical mechlorethamine as an adjuvant after completion of electron-beam therapy slightly improves survival and disease-control (fig 10). At this time, however, the numbers are too small and the followup intervals are too brief to indicate whether this improvement is significant.

Another important influence on a patient's subsequent course is his initial remission status. Survival of patients with generalized plaque disease is markedly better when they achieve an initial CR (fig 8). However, since only a small percentage of patients (10%) *fail* to achieve a CR, this parameter is useful clinically in only very few patients. In addition, the group who failed to achieve a CR consisted largely of older patients treated with lower doses.

The single most important prognostic factor is the initial extent of disease, both the severity of skin involvement and the presence or absence of extracutaneous MF. We observed clear differences in prognosis between patients with limited plaque, generalized plaque, erythematous, and tumorous lesions of the skin (figs 2 and 3). The presence of extracutaneous disease has a seriously adverse effect on prognosis (figs 4 and 5). The presence of palpable adenopathy heralds a worse prognosis and may, in fact, be the first sign of extracutaneous involvement. In the generalized plaque group, the freedom from relapse among patients with palpable adenopathy is much worse than among those without palpable lymph nodes at the time of presentation (fig 6). This observation is further detailed in table 5. Table 5 shows the current status of all patients grouped by the initial extent of skin involvement and the initial lymph node status. For

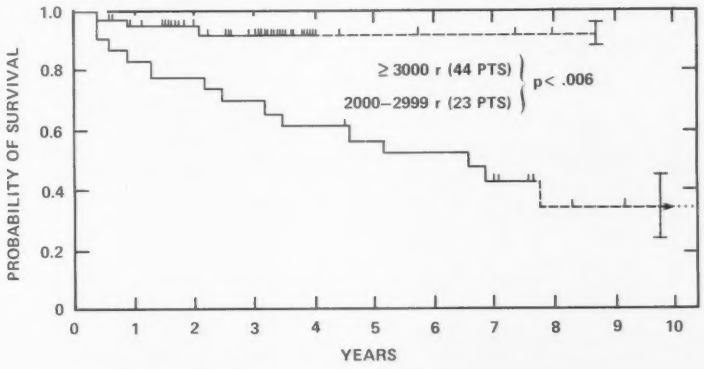

FIGURE 9.—Effects of initial dose on survival of 67 patients with generalized plaque MF. The broken lines indicate that < 5 patients are at risk.

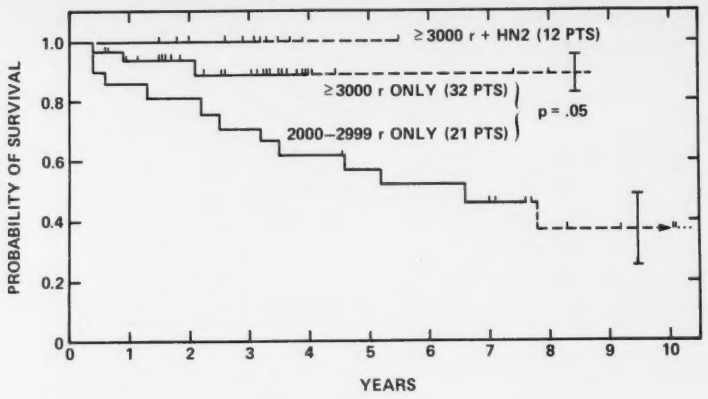

FIGURE 10.—Effects of dose and adjuvant topical mechlorethamine on survival of 65 patients with generalized plaque MF (2 patients excluded had adjuvant therapy other than topical mechlorethamine). The broken lines indicate that < 5 patients are at risk.

each extent of skin involvement, patients who had palpable lymph nodes have done more poorly than those with nonpalpable lymph nodes. Nearly two thirds of the patients who had plaque involvement only in the absence of palpable adenopathy were without evidence of disease at the time of their last followup visit. In contrast, more than half of the patients with plaque involvement and palpable adenopathy had persistent evidence of disease at the time of their last followup.

At present, total-skin electron-beam therapy is one of the single best modalities for the treatment of MF. With high initial doses of therapy, CR rates are excellent and may be maintained for periods of > 3 years. Nevertheless, even among our best prognostic groups, treatment is frequently unsuccessful. There are several possible explanations for this failure. The dose used may have been inadequate, there may be deeply situated foci of disease which lie beneath the maximum depth of penetration of

TABLE 5.—Current status of 140 patients with MF grouped by initial extent of skin involvement and presence or absence of palpable adenopathy

Extent of skin involvement	Lymph node status	No. of patients	No. of patients (%)				
			Continuously NED*	Prior relapse, now NED	Dead, NED	Alive with MF	Dead with MF
Limited plaque	Nonpalpable	20	13 (65)	4 (20)		2 (10)	1 (5)
	Palpable	5	2 (40)	2 (40)			1 (20)
Generalized plaque	Nonpalpable	31	10 (32)	5 (16)	1 (3)	8 (26)	7 (23)
	Palpable	36	7 (19)	9 (25)		10 (28)	10 (28)
Erythematous	Nonpalpable	4	2 (50)	1 (25)			1 (25)
	Palpable	17	1 (6)	5 (29)	1 (6)	5 (29)	5 (29)
Lichenoid	Nonpalpable	—					
	Palpable	2					2 (100)
Tumor	Nonpalpable	4	1 (25)			1 (25)	2 (50)
	Palpable	21	1 (5)	3 (14)		6 (29)	11 (52)
Totals	Nonpalpable	59	26 (44)	10 (17)	1 (2)	11 (19)	11 (19)
	Palpable	81	11 (14)	19 (23)	1 (12)	21 (26)	29 (36)
		140	37 (26)	29 (21)	2 (1)	32 (23)	40 (29)

*NED = no evidence of disease.

the electrons, or internal dissemination may have already taken place.

Although our success in the treatment of MF has increased since we have increased the initial dose of electron-beam therapy, normal tissue tolerance prevents any further escalation of the dose as long as we continue our current fractionation schedule. As an alternative to increasing the dose, in an effort to improve the results of therapy, the concept of a topical adjuvant or maintenance therapy after completion of electron-beam treatment holds great promise. The logical initial choice for a topical adjuvant therapy is mechlorethamine. Topical mechlorethamine alone is frequently successful in clearing the skin and we have extensive experience in its use after electron-beam therapy (7,15). At Stanford, we are currently engaged in a prospective randomized clinical trial in which patients with limited plaque, generalized plaque, or erythematous disease without the changes of dermatopathic lymphadenitis on lymph node biopsy are randomized to receive electron-beam therapy alone or electron-beam therapy followed by adjuvant topical mechlorethamine.

An alternative form of topical maintenance which looks promising is PUVA (psoralens; ultraviolet light) therapy (16). We have had recent success in treating patients with erythroderma with electron-beam therapy followed by PUVA maintenance. Many of the potential complications of PUVA therapy, however, have yet to be appreciated, and for this reason, it should remain an investigational approach.

Although topical therapies have the potential for curing patients with disease limited to the skin and will continue to play an important role in the palliation of patients with both cutaneous and extracutaneous disease, they are obviously inadequate to affect the progression of extracutaneous MF. The initial challenge in the treatment of patients with extracutaneous disease is to identify those patients who have minimal extracutaneous involvement. It is possible that internal dissemination occurs by spread of disease through regional lymph nodes. When palpable lymph nodes are biopsied, however, they frequently show only dermatopathic lymphadenitis. While such changes are considered to be benign when associated with nonmalignant skin disease, this does not appear to be the case in MF. Cytogenetic studies have confirmed the clinical impression that dermatopathic lymphadenitis may, in actuality, represent the very earliest phase of lymph node involvement by MF (17). This fact very likely explains the clinical observation that patients who present with palpable adenopathy have a worse prognosis than those without adenopathy.

After identification of extracutaneous MF, the next challenge is to treat it. The lesions of MF are very radiosensitive. If one hypothesizes that this disease spreads from the skin to the internal organs by way of the lymph nodes, then there are radiotherapeutic techniques which could easily be used in the treatment of these patients while disease is still limited to the lymph nodes. Total lymphoid irradiation with four to six-mev photons has long been used in the treatment of Hodgkin's disease and other malignant lymphomas (18). Patients who have MF with palpable adenopathy could easily be treated with a combination of total-skin electron-beam therapy and total-lymphoid irradiation. Since MF is such a radiosensitive disease, the doses of irradiation which should be used are probably less than the doses required for the treatment of other malignant lymphomas. We have recently initiated a trial at Stanford in which patients who have dermatopathic lymphadenitis are randomized to treatment between electron-beam therapy followed by topical adjuvant mechlorethamine and electron-beam therapy with concurrent total-lymphoid irradiation to a dose of 3000 rads followed by adjuvant topical mechlorethamine. While it is still too early to assess the results of this study, we have found that the combined treatment is feasible.

By the time that MF is detectable in lymph nodes by routine light microscopic sections, there is likely to be visceral dissemination as well. It seems entirely reasonable to treat such patients systemically as well as topically. These patients seem to be suitable candidates for early-phase trials of new drug agents or combinations in a study situation. Radiotherapy, however, also offers a systemic approach. Low-dose, fractionated total-body irradiation has been successfully used in the treatment of other malignant lymphomas (19). At Stanford, we are currently assessing its efficacy in patients who have lymph node or visceral involvement by MF.

Although notable advances have been made in the treatment of mycosis fungoides during the past 2 decades, there are still many areas for improvement. Further advances in the treatment of this disease, however, will probably have to await (*a*) a better understanding of its natural history, (*b*) better means for detecting early extracutaneous involvement, and (*c*) more effective systemic agents.

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Status Report of 376 Mycosis Fungoides Patients at 4 Years: Mycosis Fungoides Cooperative Group

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SUMMARY

The frequency and prognostic importance of various characteristics of patients registered by the Mycosis Fungoides Cooperative Group between November 1974 and December 1977 are reported. Variables which were considered include demographic and historical factors, symptoms, extent of disease, and other physical findings. A staging system which is based on the extent of skin involvement and the number of nodal sites clinically involved is described. Finally, a description of therapeutic results to date for patients randomized into Mycosis Fungoides Cooperative Group protocols is presented.

[Cancer Treat Rep 63:701–707, 1979]

In 1974 a registry was begun for patients with pathologically proven or clinically suspected mycosis fungoides (MF). This registry was set up by the Mycosis Fungoides Cooperative Group (MFCG) (1).[3] Patients were entered in the registry by referral to one of 20 collaborating institutions where 12 pages of forms were completed with demographic, historical, physical, and laboratory data. Pathologic material was reviewed by a panel of general pathologists and dermatopathologists[4] who serve as referees using previously agreed upon definitions (*see* report in this issue by Clendenning and Rappaport [2]) and meet on occasion to discuss the disputed cases. A modified TNM scheme was used to describe the extent of disease in each patient (table 1).

This report deals predominantly with the frequency and prognostic importance of various patient characteristics and with the results of therapy.

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[2]We appreciate the assistance of Carol E. Argyropoulos in the collection of data for this study.

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TABLE 1.—Clinical TNM scheme used to describe extent of disease in MF patients

Clinical category	Definition
T_0	No skin involvement
T_1	Plaques, papules, or eczematous patches covering < 10% of the body
T_2	Same as above but covering > 10% of the body
T_3	Tumors with or without plaques or papules
T_4	Generalized erythema alone
NP_0	No enlarged peripheral lymph nodes
NP_1	Enlarged peripheral lymph nodes
NV_0	No enlarged visceral lymph nodes
NV_1	Enlarged visceral lymph nodes
M_0	No visceral organ involvement
M_1	Visceral organs enlarged, tumorous, or functionally or radiographically abnormal

The role of certain characteristics as risk factors (as opposed to prognostic factors) is reported elsewhere in this issue by Greene et al (3). A more complete analysis of prognostic factors will appear in a separate publication.

PATIENT MATERIAL AND METHODS

This report is based on 376 patients who were registered between November 1974 and December 1977. All but 22 of these 376 patients had a pathologic diagnosis of MF confirmed by a local pathologist. The temporal relationship between pathologic diagnosis and registration varied. Two hundred and fifty-eight patients were registered after pathologic diagnosis (1 month to > 20 years), 73 at the time of diagnosis, and 17 before pathologic diagnosis. For those patients who did not have a pathologic diagnosis or who were registered before diagnosis, MF was suspected clinically. For six patients, only an approximate date of pathologic diagnosis was available. Most of the subsequent analysis is based on the 348 patients with a known date of diagnosis by a local pathologist.

In investigating the prognostic significance of the variables considered, survival time was measured from registration to death or last followup, since use of other starting points could introduce bias in such a mixed prevalence-incidence study. The use of an earlier starting point such as date of clinical diagnosis or first pathologic diagnosis would have required the inclusion of historical documents or data based upon patient recollections. One patient was excluded from the analysis because only an approximate date of death was known; 84 deaths were recorded in the remaining 347 patients. Twenty-eight of the 84 deaths were attributed to causes not directly related to MF, mainly cardiovascular and cerebrovascular disease. In almost all cases MF was present at death.

The median length of followup for the 263 patients last known to be alive was 32 months (range, 0–48 months). In the survival analyses these patients are considered to be censored observations and contribute to the survival comparisons for the length of time they were followed. For most of the analyses, death from any cause was used as the endpoint. When analyses are also presented for MF deaths only, deaths due to other causes are treated as censored observations. Since it is often difficult to determine cause of death, even with complete information, these latter analyses must be interpreted with caution.

RESULTS ON PATIENT CHARACTERISTICS

The frequency of certain patient characteristics and the associated death rates based on 347 patients are shown in table 2. The death rates are expressed as deaths/100 patient-months of followup and are especially useful for screening variables for prognostic importance when the number of patients in some categories is small. The significance levels are based on an assumed exponential distribution and should not be over-interpreted. Variables which appear to be important individually ("marginally" in statistical terms) may not be important when adjusted for other factors, and vice versa. In addition, when multiple comparisons are performed, there is an increased probability of finding results significant at the customary significance level ($P = 0.05$) by chance alone. In this paper we have not applied more involved statistical procedures which address the multiple comparison issue. Finally, the small numbers of patients possessing certain attributes led to considerable variation in the estimated death rates and reduced power for detecting real differences. For this reason, failure to find statistical significance does not necessarily mean that the variable is unimportant.

Review of demographic variables (table 2) shows that most of the patients were white and 65% were male. The median patient age at registration was 58.2 years. Death rates did not differ by sex but tended to be higher for blacks and older patients. The effect of age was less pronounced when deaths not directly related to MF were treated as censored observations, suggesting that age may not be a particularly important prognostic factor for MF itself.

Death rates for all causes of death were calculated individually for a history of tonsillectomy,

TABLE 2.—Death rates according to demographic variables, symptoms, extent of disease, and other physical findings in 347 MF patients

	Category	No. of patients	Total mos of followup	All causes of death			Deaths due to MF		
				No. of deaths	Death rate*	*P* values†	No. of deaths	Death rate*	*P* values†
Demographic variables									
Race	White	301	8022	69	0.860	0.085	44	0.548	0.025
	Black	39	1073	15	1.398		12	1.118	
	Other, unknown	7							
Age in yrs	< 40	31	832	2	0.240	0.017	2	0.240	0.314
	40–60	156	4251	33	0.776	0.004	25	0.588	0.170
	> 60	154	4075	48	1.178		28	0.687	
	Unknown	6							
Sex	Male	226	6048	55	0.909	0.929	35	0.579	0.694
	Female	121	3255	29	0.891		21	0.645	
Symptoms									
Pruritus	No	104	2930	18	0.614	0.039	11	0.375	0.052
	Yes	233	6155	65	1.056		44	0.715	
	Unknown	10							
Chills	No	300	8221	65	0.791	0.001	44	0.535	0.017
	Yes	35	830	16	1.928		10	1.205	
	Unknown	12							
Burning	No	250	6827	52	0.762	0.036	36	0.527	0.113
	Yes	82	2169	27	1.245		18	0.830	
	Unknown	15							
Malaise	No	289	8212	56	0.682	< 0.0001	43	0.524	0.012
	Yes	43	813	22	2.706		10	1.230	
	Unknown	15							
Fever	No	322	8825	72	0.816	< 0.0001	49	0.555	0.0002
	Yes	9	130	6	4.615		4	3.077	
	Unknown	16							
Extent of disease									
Clinical T category	T_0	10	304	2	0.657	< 0.0001	1	0.329	< 0.0001
	T_1	134	3925	11	0.280	< 0.0001	8	0.204	< 0.0001
	T_2	104	2869	27	0.941		19	0.662	
	T_3	55	1218	21	1.724		12	0.985	
	T_4	43	946	23	2.431		16	1.691	
	Unknown	1							
No. of positive nodal sites	0	185	5425	27	0.498	< 0.0001	18	0.332	< 0.0001
	1	46	1128	9	0.798	< 0.0001	5	0.443	< 0.0001
	2–4	83	2033	30	1.476		19	0.935	
	5+	25	542	13	2.399		11	2.030	
	Unknown	8							
Other physical findings									
Erosion	No	315	8457	71	0.840	0.042	46	0.544	0.023
	Yes	32	846	13	1.537		10	1.182	
Ulcers	No	314	8575	67	0.781	< 0.0001	45	0.525	0.001
	Yes	33	728	17	2.335		11	1.511	
Telangiectasia	No	302	7790	75	0.963	0.168	47	0.603	0.969
	Yes	45	1513	9	0.595		9	0.595	
Alopecia	No	309	8392	66	0.786	0.0003	46	0.548	0.042
	Yes	38	911	18	1.976		10	1.098	
Lymphedema	No	337	9026	81	0.897	0.749	54	0.598	0.794
	Yes	10	277	3	1.083		2	0.722	

*Death rate = deaths/100 patient-mos of followup.

†Based on an assumed exponential distribution in each category. When 2 *P* values are given, the 1st refers to a test of heterogeneity of rates and the 2nd refers to a progressive trend in rates.

fungal infections, herpes simplex, warts, eczema, hay fever, asthma, contact reaction, drug reaction, food reaction, and hives. None of these variables yielded significant differences in death rates when evaluated one at a time.

Each of five symptoms (doubtless correlated) present at registration was associated with increased death rates (table 2). It is not surprising that fever showed an impressive effect on prognosis, but only nine of these patients were febrile at registration. Similarly, one might have anticipated that malaise, possibly a symptom of debility, would show a relation to death rate. The effects of pruritus, chills, and burning were less pronounced.

Extent of disease and certain physical findings at registration were strongly prognostic (table 2). The extent of skin involvement, clinical T category, was very strongly related to prognosis and a significant trend was apparent from T_1 to T_4. The same observations apply to the number of nodal sites thought to be involved clinically. Ulcers, alopecia, and erosion were each associated with increased death rates. No relation was found with lymphedema, but little can be concluded since only ten patients had this feature. Telangiectasia was not significantly associated with death rate, although if any tendency existed, patients with this feature had a lower death rate.

Since clinical T category and number of nodal sites (N) were each strongly related to prognosis, patients were cross-classified with respect to these two variables and the death rates (all causes) were computed (table 3). Ten patients had a pathologic diagnosis of MF but happened to be clear of skin involvement at the time of registration. These T_0 patients were combined with the T_1 category. Although patients with five or more sites of enlarged lymph nodes had a higher death rate than those with two to four sites, we grouped all patients with two or more sites. The subcategories in the cross-classification fall into groups according to similar prognosis as suggested in table 3. These groups may be regarded as the basis of a staging system for MF. The stages are defined as: stage I ($T_{0-1}N_{0-1}$), stage II ($T_{0-1}N_{2+}$ and T_2N_{0-1}), stage III (T_2N_{2+} and T_3N_{any}), and stage IV (T_4N_{any}). Death rates for the four stages were 0.203, 0.595, 1.740, and 2.361, respectively. Actuarial survival curves constructed for these suggested stages are presented in figure 1. The effect of other variables we have described may be less important when adjusted for stage based on T and N, a subject we will pursue in a separate publication.

TABLE 3.—Death rates* by clinical T category and No. of nodal sites

No. of nodal sites clinically involved	Death rate for clinical T category—							
	T_0-T_1		T_2		T_3		T_4	
0	I†	0.199 (6/100)	II	0.532 (9/55)	III	1.629 (8/21)	IV	1.794 (4/9)
1	I	0.238 (1/16)	II	0.696 (3/16)	III	0.995 (2/10)	IV	4.000 (3/4)
2+	II	0.679 (5/26)	III	2.113 (15/32)	III	1.616 (8/21)	IV	2.366 (15/29)

*Death rate = deaths (all causes)/100 patient-mos of followup; Nos. in parentheses = No. of deaths/No. of patients in analysis.
†Roman numerals = staging system.

THERAPY RESULTS

Although some information was available on treatment, the comparison of different therapies in such a data base is likely to be misleading. The usual difficulties in performing proper adjusted analyses are compounded by factors such as the combined retrospective and prospective nature of the data, the absence of information concerning why a specific therapy was chosen, the fact that several therapies were used at varying times, and even the uncertainty concerning when MF began or progressed. As an example of potential problems with such comparisons, a therapy which is actually beneficial may only be given to patients whose condition in some unmeasured way is perceived as worsening. This therapy may therefore appear inferior to another therapy given more routinely. Comparisons in nonrandomized studies can be criticized even in diseases where prognostic factors are relatively well-defined; in MF such comparisons are particularly ill-advised.

On the other hand, information is available on 54 patients who were randomized in MFCG protocols. The number of patients is too small for the results to be discussed statistically, but the data are presented because there are so few reports of patients with MF who have been randomized to receive therapy and because certain trends may be of interest, particularly if seen in other studies.

All patients had pathologically confirmed MF. They were assigned to one of three groups based on extent of disease at the time of randomization (table 4). Patients in group A either had $< 10\%$ of their surface area covered by eczematous patches or plaques and may or may not have had palpable lymph nodes (T_1NP_0 and T_1NP_1) or had $> 10\%$ covered but did not have lymphadenopathy (T_2NP_0). All patients had a biopsy of a palpable lymph node or a "blind" biopsy of a draining node if none was

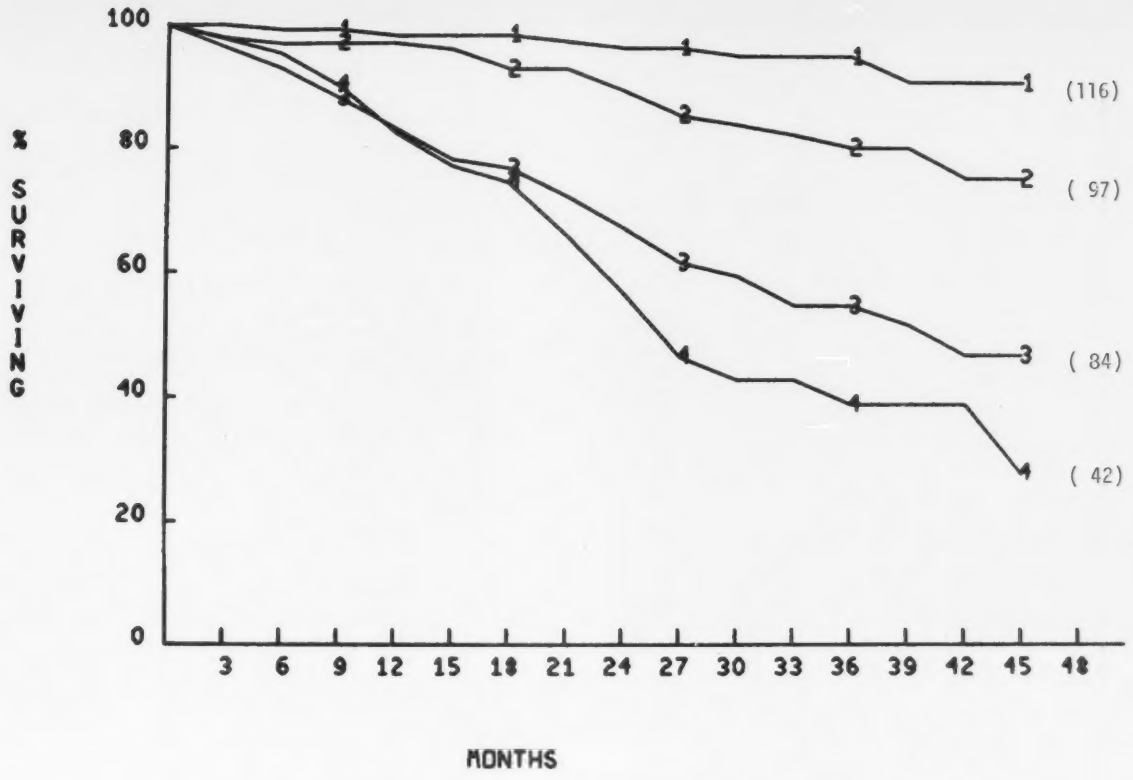

FIGURE 1.—Actuarial survival curves (%) for disease stages based on clinical T category and No. of nodal sites clinically involved. Curves numbered 1–4 = stages I–IV. Nos. in parentheses = No. of patients.

TABLE 4.—Treatment groups for MFCG protocols

	Extent of disease			
Group	T*	NP*	Lymph node pathology	Protocol
A	T_1	Any	Negative or DL	Electron beam vs mechlorethamine vs both
	T_2	NP_0	Negative or DL	
B	T_2	NP_1	Negative or DL	Electron beam + mechlorethamine vs electron beam + CHOP
	T_3	Any	Negative or DL	
C	T_4	Any	Any findings	MTX + CF vs MTX + CF, Adriamycin, and bleomycin
	Any T	Any	MF	

*See table 1 for explanation.

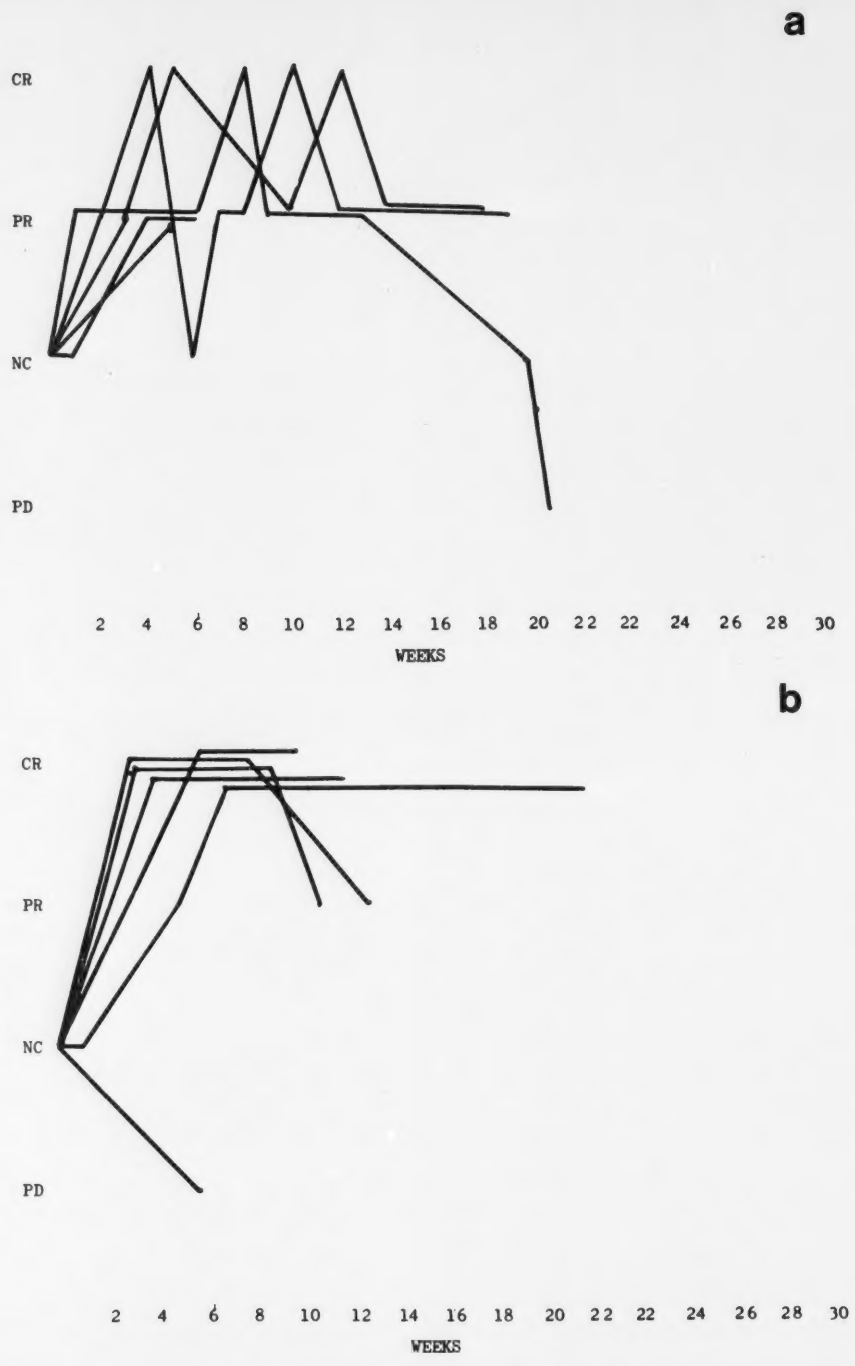

FIGURE 2.—Duration of response in (*a*) patients given electron-beam therapy followed by topical mechlorethamine and (*b*) patients given electron-beam therapy followed by CHOP.

palpable. Pathology was negative for MF or showed only dermatopathic lymphadenitis (DL) for inclusion in group A. Supraclavicular or axillary lymph nodes were preferred to femoral or inguinal nodes. Patients randomized in group A received either (*a*) 3500 rads of electron-beam therapy following the six-position Stanford technique or (*b*) daily total-body painting with 10 mg of mechlorethamine without previous attempts to hyposensitize or (*c*) a combination in which the full course of electron-beam therapy was followed 1 month later by topical mechlorethamine. The topical mechlorethamine was not discontinued but was used less frequently if the disease subsided. Endpoint was recurrence or extension of disease.

Group B patients were those who had either extensive skin involvement and enlarged lymph nodes (T_2NP_1) or three or more tumors (T_3) regardless of the presence or absence of adenopathy. Although the lymph node biopsy was negative or showed only DL in group B patients, these patients were not expected to do as well as those in group A. Patients in group B were randomized to receive either the combined topical electron-beam therapy followed by topical mechlorethamine or electron-beam therapy followed by systemic chemotherapy. The chemotherapy protocol was an attenuated CHOP regimen and consisted of cyclophosphamide at a dose of 500 mg/m^2 iv, Adriamycin at a dose of 40 mg/m^2 iv, and vincristine at a dose of 1.4 mg/m^2 iv (maximum dose, 2 mg), all given on Day 1, and prednisone at a dose of 60 mg/m^2 given on Days 1–5. The course was to be repeated every 21 days for six courses.

Patients with visceral disease including those with MF confined to the lymph nodes and those with the Sézary syndrome were classed in group C. The data from patients with the Sézary syndrome were examined separately. Patients in group C were randomized to receive systemic chemotherapy protocols but were allowed to have additional topical therapy or radiotherapy to reduce tumor load. Therapy arms consisted of either 500 mg/m^2 of methotrexate (MTX) and citrovorum factor (CF) (at 5% of the MTX dose) repeated every 3 weeks or 250 mg/m^2 of MTX and CF at the same percentage dose, 45 mg/m^2 of Adriamycin on Day 15, and 5–8 mg/m^2 of bleomycin on Days 15 and 22. This course was repeated every 4 weeks. Three courses were given unless the patient showed a response, in which case therapy was continued.

The results are as follows. Twenty-one patients were classed in group A with minimal disease confined to the skin. Six of eight patients randomized to receive electron-beam therapy had a clearing of their disease but none maintained the remission (followed for 6 months) without the addition of topical mechlorethamine. Four of eight patients treated with mechlorethamine have maintained their remission for at least 6 months. The combination of electron-beam therapy followed by topical mechlorethamine was a recent addition to the treatment protocol. Three patients received this treatment and all had a complete remission, with two maintaining that remission at 4 months. Two patients were not evaluable.

Group B consisted of 15 patients but only 11 were in the protocols long enough to be evaluated. Patients treated with the combined topical therapy arm had short remissions while those given electron-beam and systemic chemotherapy followed a different course (fig 2). In two patients in the latter group in whom early recurrences did develop, the recurrences were associated with premature discontinuation of chemotherapy. In general, the patients in this arm did better than those in group A although disease in group B patients was more extensive at the outset.

Group C, excluding the five Sézary cases, consisted of 13 patients. Two thirds of the non-Sézary patients had a partial but none had a complete response to any of the systemic chemotherapy regimens. There was no response to therapy in any of the patients with Sézary syndrome and two died within the first 2 months of treatment.

Registration of new cases is now restricted to those patients eligible for randomized protocols. Followup of registered cases will be continued at yearly intervals and updates will be reported as trends develop.

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Scandinavian Mycosis Fungoides Trial

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SUMMARY

One hundred and nineteen patients (70 males and 49 females) with mycosis fungoides have been entered in a study conducted by the Scandinavian Mycosis Fungoides Cooperative Study Group which has been in operation since 1974. There were five stages based on histology, clinical examination, hematology, chest roentgenogram, skin, liver, and lymph node biopsies, and bone marrow examination. Seventy-three patients were in stage II (cutaneous plaque stage), 29 patients were in stage III (cutaneous tumor stage), 11 patients were in stage IV (lymph node involvement), and six patients were in stage V (visceral involvement). Twenty-six patients are now dead. Various treatment modalities have been used. Topical mechlorethamine has been used in 21 patients with stage II disease resulting in a complete response (CR) in ten patients and a partial response (PR) in nine. However, many relapses occurred because of insufficient maintenance therapy. PUVA (8-methoxypsoralen and ultraviolet light) was used in 26 patients with stage II disease, resulting in a CR in 17 patients and a PR in eight. Twelve patients with stage III disease also received PUVA, resulting in a CR in six patients and a PR in three. Nine patients with stage III–V disease were treated with im bleomycin at a dose of 15 mg twice weekly for 7 weeks. Three patients had a CR and two patients had a PR, but relapses usually occurred soon thereafter. Bleomycin at a dose of 15 mg twice weekly plus methotrexate at a dose of 15 mg/m²/week for 7 weeks produced a CR in one patient and a PR in eight, but toxicity was high and relapses soon occurred. VP-16-213 produced a CR in two of nine patients with advanced disease and a PR in three patients. Prednimustine was given to five patients and produced a PR in two. It is concluded that topical and systemic therapy should be combined for the treatment of this disease.

[Cancer Treat Rep 63:709–711, 1979]

The Scandinavian Mycosis Fungoides Cooperative Study Group has been in operation since 1974. The group consists of 14 dermatologic departments in Denmark, Norway, and Sweden. The three countries have a population of 17 million. We believe that our group receives all of the mycosis fungoides (MF) patients from Denmark, and a major proportion of the patients with MF in Norway and Sweden are entered in the group project.

Workup of new patients with MF includes hematologic examination with liver and kidney function tests, chest roentgenogram, immunologic examination (tuberculin test and dinitrochlorobenzene), skin, liver, and lymph node biopsies (if palpable lymph nodes are present), and further bone marrow examination. Liver, spleen, and bone scanography and lymphangiography are performed even though these procedures usually give negative results in early stages of the disease.

There are five stages used by the Scandinavian Mycosis Fungoides Cooperative Study Group: stage II is the plaque stage, stage III is the tumor stage with ulcerations, stage IV indicates lymph node involvement, and stage V indicates visceral involvement. Apart from these stages we have encountered some patients with tumors with a monomorphous infiltrate, a more acute course, and a poor prognosis. These patients were formerly considered to have

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"d'emblé" MF, but we have now decided to label this entity malignant lymphoma of the skin, a disease entity that perhaps should be handled in a different way from classic MF.

One hundred and nineteen patients (70 males and 49 females) were treated with one of several treatment protocols. When entered in the study, 73 patients were in stage II, 29 were in stage III, 11 were in stage IV, and six were in stage V. Twenty-six patients are now dead.

Several treatment modalities have been used. In the cutaneous forms of MF, topical mechlorethamine, PUVA (8-methoxypsoralen and ultraviolet light), and electron-beam therapy were used. In the patients with tumors and in the patients with extracutaneous involvement, systemic chemotherapy with bleomycin, bleomycin plus methotrexate, VP-16-213, prednimustine, cyclophosphamide combined with PUVA, CAVOP,[2] and finally transfer factor were used in addition to other protocols. Data from some of these protocols are reported below.

Whole-body topical application of mechlorethamine has been used in 21 patients in plaque stage with excellent results (table 1), but in many patients recurrence of disease occurred due to insufficient maintenance therapy, which has now been enforced (1).

PUVA was used in 26 patients in plaque stage with good results and with remission maintenance for up to 2 years. In patients with tumors (stage III), the results were less satisfying and many patients relapsed (table 2).

In patients with advanced tumor stage and in patients with extracutaneous involvement, im bleomycin was given twice weekly for 7 weeks to nine patients (table 3). Remission was induced in five patients but it was of short duration (2).

The combination of im bleomycin and methotrexate produced better results (table 4), but remissions did not last long and the toxicity was high with many deaths (2).

VP-16-213 has been used in nine patients with a good remission rate, but remissions were of short duration and the treatment had high toxicity (table 5) (3).

Prednimustine is a combination of chlorambucil and prednisolone and it can be given in high doses.

TABLE 1.—21 patients with stage II MF treated with topical whole-body application of mechlorethamine

Dose	20 mg/40 ml of water/m²
Schedule	
Induction therapy	qd × 15 days
Maintenance therapy	1 dose/mo
No. of patients with—	
CR	10
PR	9
No change	0
Progressive disease	2

TABLE 2.—26 patients with stage II MF and 12 patients with stage III MF treated with PUVA

Induction schedule	4 doses/wk
Maintenance schedule	2 doses/wk
No. of stage II patients with—	
CR	17
PR	8
No change	1
No. of stage III patients with—	
CR	6
PR	3
No change	2
Progressive disease	1

TABLE 3.—9 patients with stage III–V MF treated with im bleomycin*

Dose and schedule	15 mg × 2–7 wks
No. of patients with—	
CR	3
PR	2
No change	1
Progressive disease	3

*All responses were short-lived.

TABLE 4.—10 patients with stage III–V MF treated with the combination of im bleomycin and methotrexate*

Dose and schedule of—	
Methotrexate	15 mg/m² × 1–7 wks
Bleomycin	15 mg × 2–7 wks
No. of patients with—	
CR	1
PR	8
No change	1

*All responses were short-lived.

TABLE 5.—9 patients with stage III–V MF treated with VP-16-213*

Dose and schedule of—	
Induction therapy	100 mg iv × 5 days q3wks
Maintenance therapy	100 mg orally × 5 days q3wks
No. of patients with—	
CR	2
PR	3
No change	4

*All responses were short-lived.

[2]CAVOP = cyclophosphamide, adriamycin, vincristine, VP-16-213, and prednisone.

It has only been tried in five patients with no encouraging results thus far (table 6) (4).

CAVOP is a protocol recently activated and is designed for patients with advanced disease. The results are not yet available.

At present, we are of the opinion that it is possible to control early stages of MF but the tumor stage is difficult to handle and extracutaneous forms of the disease have a poor prognosis. In such cases we think it is important to combine topical and systemic therapy since we have seen patients with extracutaneous spreading despite apparent cure of the cutaneous disease (5,6); we feel it is necessary to start this combination therapy in patients who already have early-stage tumor.

We have come to the conclusion that early and aggressive therapy for MF is mandatory.

TABLE 6.—5 patients with stage III–V MF treated with prednimustine (chlorambucil plus prednisolone)

Dose and schedule	120 mg/m² orally × 5 days q3wks
No. of patients with—	
PR	2
No change	3

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Combined Modality Therapy With Electron-Beam Irradiation and Systemic Chemotherapy for Cutaneous T-Cell Lymphomas

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The optimal treatment for patients with cutaneous T-cell lymphomas (CTCL), including mycosis fungoides and the Sézary syndrome, is not known. Several forms of therapy including topical chemotherapy (1–7), radiation therapy (especially electron-beam) (8–19), systemic chemotherapy (20–25), and photochemotherapy with psoralen and ultraviolet A light (PUVA) (26–30) have produced regression of lesions in a majority of treated patients. Results from each of these therapies applied individually are well-represented in this issue. Unfortunately, the duration of remission is limited. Electron-beam irradiation, topical mechlorethamine, and PUVA have produced long-term remissions. However, except for a few patients treated with topical mechlorethamine, only electron-beam therapy has produced continuous disease-free survival when therapy is stopped. These long-term remissions are generally limited to patients with early cutaneous disease. Possible explanations for the inability of these therapies to cure patients include the following: (*a*) The therapy cannot be applied to all areas of cutaneous disease. Since the body surface has many irregular contours, it is difficult if not impossible to treat the entire skin surface uniformly with electron-beam irradiation, topical chemotherapy, or PUVA. Relapses in underdosed areas of skin after electron-beam radiation therapy are well-documented. (*b*) The disease is systemic in nature at the time of treatment, while the treatment is directed only at the skin. Several lines of evidence which suggest the early systemic nature of CTCL are reviewed elsewhere in this issue (31–33). In addition, there is evidence that the circulating tumor cells in the Sézary syndrome arise from noncutaneous sites (34). (*c*) Cell-kill from the therapy is insufficient to lead to cure and/or resistance develops during therapy.

Combined modality therapy with total-body electron-beam irradiation and systemic chemotherapy is an approach which theoretically can eliminate the causes of failure listed above. At the National Cancer Institute, 39 patients with CTCL were treated with the combined modality approach and the preliminary results are presented.

METHODS AND MATERIALS

Thirty-nine patients with histologically confirmed mycosis fungoides or Sézary syndrome were entered in the study conducted at the National Cancer Institute-Veterans' Administration Medical Oncology Branch between July 1976 and November 1978. Patients previously treated with systemic chemotherapy or electron-beam irradiation were ineligible. Patients who had previously received topical or oral corticosteroids, topical chemotherapy, PUVA, or local radiation treatments were not excluded. The pertinent patient characteristics are provided in table 1.

Pretreatment staging evaluation included: complete history and physical examination, whole-body photographs, complete blood count and differential, SMA-12, chest roentgenogram, lymphangiogram, ^{99m}Tc liver-spleen scan, bone marrow aspiration and biopsy, percutaneous liver biopsy, peritoneoscopy with multiple liver biopsies (if percutaneous biopsy was negative), and lymph node biopsy (if adenopathy was present). Patients were staged according to a modified classification first proposed by Van Scott et al (1) (table 2). Treatment regimens are shown in figure 1. Patients with disease confined to the skin

TABLE 1.—Patient characteristics

No. of patients in study	39
Male/female	23/16
White/black	28/11
Median age in yrs (range)	53 (22–75)

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TABLE 2.—Staging classification

Stage	Description
I	Limited plaques (< 10% of body surface), no adenopathy
II	Generalized plaques (≥ 10% of body surface), no adenopathy
III	Cutaneous tumors, no adenopathy
IV	Lymphadenopathy with any skin stage
V	Visceral involvement with any skin stage

(stages I and II) were treated with whole-body electron-beam irradiation and three separate 2-week courses of iv mechlorethamine. The electron-beam therapy was given by a dual-field rotating-table technique employing 3.2-mev electrons delivered from a Linac 18 (Varian Corp, Palo Alto, Calif). The top of the head, perineum, and bottom of the feet were treated with "boost" electron therapy. Patients with advanced disease (stages III–V) were treated with simultaneous electron-beam radiotherapy and systemic combination chemotherapy. The same electron-beam techniques were utilized. Weekly iv chemotherapy with vincristine, Adriamycin, and bleomycin (VAB) was given on the afternoon of the day the patient received electron-beam therapy. Oral chemotherapy with cyclophosphamide, methotrexate, and prednisone (CMP) was given at the completion of electron-beam and VAB therapy. The VAB-CMP chemotherapy was then continued until three cycles (54 weeks) were completed. At 54 weeks, patients were restaged. Patients in complete remission had all therapy discontinued; those with partial remissions continued to receive VAB-CMP chemotherapy. Chemotherapy was discontinued at 18 weeks in patients with no response or at the time of disease progression in any patient.

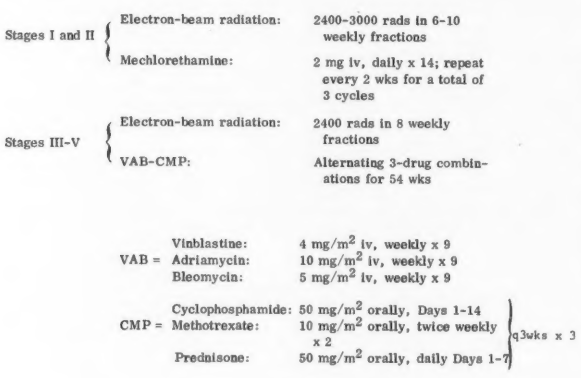
Stages I and II
Electron-beam radiation:
2400–3000 rads in 6–10 weekly fractions
Mechlorethamine:
2 mg iv, daily x 14; repeat every 2 wks for a total of 3 cycles
Stages III–V
Electron-beam radiation:
2400 rads in 8 weekly fractions
VAB-CMP:
Alternating 3-drug combinations for 54 wks
VAB =
Vinblastine: 4 mg/m² iv, weekly x 9
Adriamycin: 10 mg/m² iv, weekly x 9
Bleomycin: 5 mg/m² iv, weekly x 9
CMP =
Cyclophosphamide: 50 mg/m² orally, Days 1–14
Methotrexate: 10 mg/m² orally, twice weekly x 2
Prednisone: 50 mg/m² orally, daily Days 1–7
q3wks x 3

FIGURE 1.—Therapeutic schema.

A complete response was defined as complete disappearance of all evidence of disease both clinically and histopathologically. A partial response was defined as marked improvement in skin lesions agreed upon by at least two observers and/or a 50% decrease in the product of the perpendicular diameters of other lesions, including lymph nodes and hepatic lesions, without the development of any new lesions or progression of any existing lesions. Disease progression was defined as the development of any new lesions, a 50% increase in the perpendicular diameters of any measurable lesions, or significant worsening of skin lesions.

RESULTS

The number of patients in each stage and their therapeutic responses are provided in table 3. The objective response rate is 97% with 57% complete responders and 40% partial responders. The complete remission rate is higher in patients with disease confined to the skin (stages I and II) than in patients with more advanced disease: 86% versus 39% respectively. At present, with a median followup of 19 months, only two of the 12 complete responders in stages I and II have had recurrences, compared to seven recurrences among nine complete responders in stages III–V. The actuarial survival of patients with stages I and II disease is shown in figure 2 and is compared with survival after topical mechlorethamine reported from Temple University in patients with stages I and II (2) and after electron beam radiotherapy at Stanford University in patients without adenopathy (8). There are no obvious differences between these curves during the first 2 years of followup. Obviously, a much longer observation period is required before meaningful conclusions can be drawn. Currently, ten of 14 stage I and II patients remain alive and disease-free.

The actuarial survival of patients with stages III–V from the National Cancer Institute and from Temple University after topical and/or iv mechlorethamine (2) and the survival of patients with adenopathy from Stanford University after electron beam irradiation (8) are shown in figure 3. The 2-year actuarial survival in our series was 88% compared with about 60% at Stanford and Temple Universities.

Toxicity

The most frequent side effects of the combined modality treatments have been acute skin toxic reactions due to the radiation. These range from mild erythema to moist desquamation and/or ulcer formation. Mild erythematous reactions have oc-

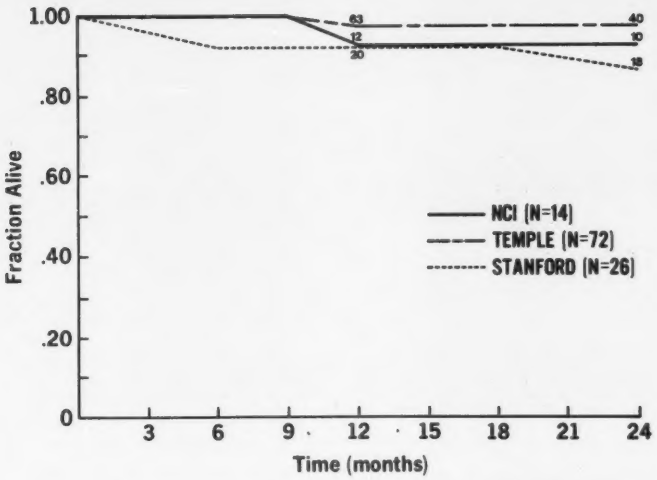

FIGURE 2.—Actuarial survival for patients with limited or generalized plaque disease without adenopathy (stages I and II). Results from this trial are compared to published results from Stanford University (stage II) after electron beam irradiation (8) and from Temple University (stages I and II) after topical mechlorethamine (2). N = No. of patients in each trial; at 1 yr, 12, 63, and 20 patients were at risk, and at 2 yrs, 10, 40, and 18 were at risk in the NCI, Stanford, and Temple series respectively. Nos. at 12 and 24 mos are the Nos. of patients at risk at each time point.

curred in the majority of patients, and more severe reactions requiring hospitalization have occurred in ten patients. Patients receiving simultaneous combination chemotherapy and electron-beam radiation therapy have not had any obvious increase in skin toxicity. Patients with fair skin and/or the Sézary syndrome have had more skin toxicity. Chronic skin changes including telangiectasis, atrophy, and dryness have also occurred in a significant fraction of patients. Gynecomastia and excess tearing have developed in some patients. Significant myelosuppression (wbc count $< 2000/mm^3$) has developed in a minority of patients receiving iv mechlorethamine. Significant myelosuppression (wbc count $< 2000/mm^3$) has also been uncommon in patients receiving the combination chemotherapy. No deaths from either radiation or chemotherapeutic toxicity have occurred.

DISCUSSION

Although followup of patients in this study is too short to fully establish the efficacy of combined modality therapy, several preliminary conclusions can be drawn. Complete remissions are observed in almost all patients with stage I and II disease and in a significant fraction of patients with lymphadenopathy and/or visceral disease. The fraction of patients with stage I and II disease remaining

TABLE 3.—Therapeutic results by stage

Stage	Total No. of patients	No. of patients with—			No. of patients not evaluable (< 4 mos of therapy)
		Complete remission	Partial remission	No remission	
I	5	4	1	0	0
II	9	8	1	0	0
III	1	1	0	0	0
IV	19	6	11	0	2
V	5	2	2	1	0
	39	21	15	1	2

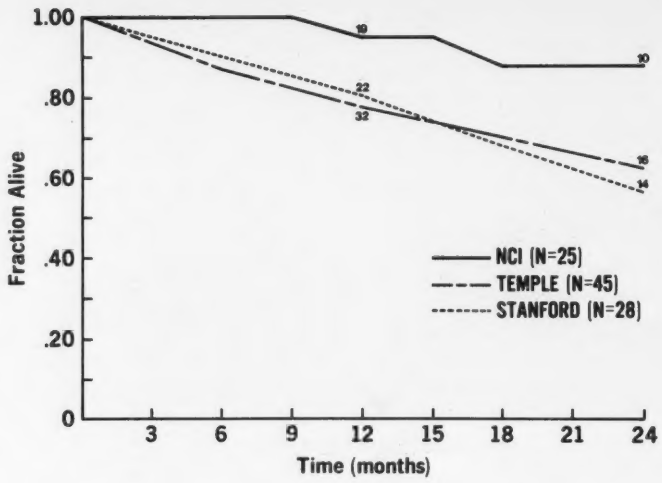

FIGURE 3.—Actuarial survival for patients with advanced disease (stages III–V). Results from this trial are compared to published results from Stanford University (patients with generalized plaques and adenopathy) after electron beam irradiation (8) and from Temple University (patients with cutaneous tumors, adenopathy, and visceral involvement) after topical and/or iv mechlorethamine (2). N = No. of patients in each trial; at 1 yr, 19, 22, and 32 patients were at risk, and at 2 yrs, 10, 14, and 16 were at risk in the NCI, Stanford, and Temple series respectively. Nos. at 12 and 24 mos are the Nos. of patients at risk at each time point.

disease-free (ten of 14) is high but the followup is short. Comparisons of survival between different centers is often difficult because of differences in staging procedures, staging classification, and prognostic variables in the groups. Since none of our patients with limited or generalized plaques and no adenopathy (stages I and II) were upstaged by the staging procedures, comparison with similar patients at Stanford and Temple Universities is not unreasonable. For stage I and II patients there are no striking survival differences at 2 years. It will be necessary to determine the 5-year disease-free survival and the 10-year overall survival before any differences would be apparent. The survival of patients with extracutaneous disease may be improved by the addition of combination chemotherapy in comparison with patients at Stanford University treated with electron-beam therapy alone or patients at Temple University treated with topical mechlorethamine. Unfortunately, the majority of patients with extracutaneous disease who achieve complete remission and have therapy discontinued will also have recurrence. It is too early to determine how many of these patients will achieve a second complete remission when therapy is reinstituted. For stages III–V the durations of both partial remissions (median, > 12 months) and complete remissions (median, > 21 months) are longer than those reported for single-agent chemotherapy.

The toxicity from combined modality therapy is acceptable even when the two modalities are given simultaneously. Extreme attention to detail must be given in following cutaneous toxicity while electron-beam therapy is delivered. Cutaneous toxicity is not strikingly different in patients receiving the combination chemotherapy.

While this trial demonstrates the capabilities of delivering combined modality therapy, it also underscores the difficulties in interpretation of therapeutic results. There is an obvious need for long observation periods. Furthermore, the need for prospective randomized trials of conservative single modality therapy versus intensive combined modality therapy is evident.

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Report of the Committee on Pathology of Cutaneous T Cell Lymphomas [1]

William E. Clendenning[2,*] and Henry W. Rappaport[3]

The recent advances, current status, and problems in the diagnosis of cutaneous T cell lymphomas are briefly reviewed. The questions considered and the recommendations made by the committee are given.

REVIEW OF THE PATHOLOGY OF CUTANEOUS T CELL LYMPHOMAS

The pathology of T cell lymphomas remains a difficult and problematic field in which reasonable "experts" may have profound differences (1,2). Therefore, at this time one cannot provide or expect absolute or definitive pathologic criteria for diagnosis about which there will be no disagreement. The diagnosis of cutaneous T cell lymphomas still requires close interaction between the experienced clinician and the pathologist. This state of affairs may be distasteful to the purist and more or less disturbing to the scientist, but it reflects reality and will not change until a definitive marker of the disease is found. Thus, the present situation must be faced realistically; this is that the clinician makes the diagnosis before the pathologist in the majority of cases—at a time when the best the pathologist can objectively do is say "atypical infiltrate with features suggesting cutaneous T cell lymphoma." In a minority of cases the diagnosis may be reached more or less concurrently. Relatively rarely will the pathologic diagnosis antedate clinical suspicion. The latter situation is fraught with hazard because pathologic simulants of cutaneous T cell lymphoma are not uncommon (3). For example, biopsies of skin papules caused by the scabies mite or of intense contact dermatitis reactions may be essentially indistinguishable pathologically from cutaneous T cell lymphoma.

What have been the significant advances in the pathology of cutaneous T cell lymphoma in the past decade? Without question, the most important is the recognition that the proliferative cell is a lymphocyte of thymic origin (4,5). This has evolved through electron-microscopic studies involving the Sézary variant (6) and the work of many investigators in further defining the T cell nature of these lymphocytes (7–10). Concurrently, light- and electron-microscopic morphologic studies have defined the importance of recognizing the hyperconvoluted nuclear membrane of this proliferative lymphocyte to facilitate diagnosis (6,11–13). At the same time there has been recognition that this cell may be seen in a number of benign skin disorders and, therefore, that this specific cellular morphology does not in and of itself signify a malignant lymphomatous process (14).

The pathology of the extracutaneous involvement of cutaneous T cell lymphoma has received the attention it has always deserved but not previously received. The papers of Rappaport and Thomas (11), Rosas-Uribe et al (12), and Long and Mihm (15) are significant in this regard.

There still seems too little willingness to recognize that variations in morphology in cutaneous T cell lymphoma more likely reflect variations in the immunologic responses of the host (the patient) to a neoplastic or preneoplastic process or the temporal development of more aggressive neoplastic features by the proliferative lymphocyte, rather than separate clinicopathologic entities. Thus, debate still rages over the Sézary variant, and a tendency persists to speak of the "evolution" of cutaneous T cell lymphoma into Hodgkin's disease, lymphocytic lymphoma, or leukemia (2). The value of defining leukemic variants of cutaneous T cell lymphoma (16) on the basis of cell size remains to be determined in a clinical and therapeutic sense. This work has certainly enhanced pathologic diagnostic recognition.

Differences in interpretation of the same case emphasize the need for a central pathology registry office and a consultant panel to serve all mycosis fungoides (MF) studies, particularly therapy trials.

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[1]The Committee on Pathology of Cutaneous T Cell Lymphomas consisted of the following members: William E. Clendenning and Henry W. Rappaport (*Workshop Co-Chairmen*) and H. Azar, W. Caro, B. Fischmann, A. Gazdar, L. Golitz, J. Guccion, E. Helwig, E. Jaffee, M. Matthews, H. Rowden, G. Schechter, D. Variakojis, J. Whang-Peng, and D. Zucker-Franklin.

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Similar definitions and diagnostic criteria must be used if survival and morbidity data are to be compared between studies. One attempt to do this has been conducted by the Mycosis Fungoides Cooperative Group whose Pathology Panel has evolved a glossary of histopathologic terms and a working set of pathologic definitions for the various stages of cutaneous T cell lymphoma to provide a basis for future registry and panel work (*see* Appendix). Histologic features most useful for diagnosis and some clinicopathologic correlations were presented by Caro et al at the workshop.

QUESTIONS CONSIDERED BY THE PATHOLOGY COMMITTEE AND RECOMMENDATIONS

Questions

The goal of the pathology committee of this workshop was to answer the first two of the following three questions and to offer suggestions for the third question.

(*a*) What are the basic service requirements of a central pathology registry office?

(*b*) What are the working definitions and histopathologic criteria?

(*c*) What are the specific research endeavors which appear most promising and which a central pathology registry office should undertake either itself or collaboratively?

Recommendations

Skin

(*a*) It was agreed that the central registry office would continue to receive specimens in formalin-fixed, paraffin-embedded blocks.

(*b*) It was agreed that a minimum of six sections from a specimen should be examined before a diagnosis is rendered by the central registry team composed of a pathologist and a dermatopathologist.

(*c*) It was agreed that if the diagnosis made by the central registry pathology team agrees with the diagnosis from the collaborating institution, then routine work may stop at this point. However, if the central registry pathology team diagnosis disagrees with the diagnosis of the collaborating institution, then slides should be sent to two consultant panel members before a consensus diagnosis is rendered for registry and statistical purposes.

(*d*) The definitions and glossary prepared by the present Pathology Panel of the Mycosis Fungoides Cooperative Group (Appendix) were found generally acceptable to the group. It was agreed that three previously used diagnostic categories (chronic dermatitis with features suggesting MF, atypical cellular infiltrate, and atypical cellular infiltrate suggesting MF) would be combined in one category for future registry and statistical purposes.

(*e*) Minor changes in the pathology forms now in use were proposed by Dr. Caro and accepted by the group.

Lymph Nodes

It was agreed that one of the most important issues is the establishment of criteria for the diagnosis of lymph node involvement by MF. A question was raised as to whether the recognition of cells with hyperconvoluted ("cerebriform") nuclei, when present singly or in clusters of three to six, is diagnostic of MF and whether it is a reproducible finding. While information is presently available that hyperconvoluted cells may occur in the skin of patients with dermatoses other than MF, no similar observations have been reported in the lymph nodes of patients with dermatopathic lymphadenitis not associated with MF. It was therefore suggested: (*a*) that the files of the Armed Forces Institute of Pathology be searched for cases of dermatopathic lymphadenopathy from patients who had MF or subsequently developed MF and for an equal number of cases of dermatopathic lymphadenopathy in which MF could be ruled out with certainty after a sufficiently long followup period; (*b*) that excellent sections from these cases be sent unidentified to several pathologists including those involved in the MF study carried out by the National Cancer Institute (NCI)-Veterans' Administration Medical Oncology Branch at the Veterans' Administration Hospital (Washington, DC); and (*c*) that these sections be classified as LN-0 to LN-4, according to the criteria proposed by the pathologists involved in the NCI trial (fig 1).

The purpose of this double-blind study is to determine whether dermatopathic lymphadenopathy in patients with MF can be distinguished from dermatopathic lymphadenopathy in patients without MF, and whether hyperconvoluted cells in small numbers may be evident in patients with dermatopathic lymphadenopathy without MF. If it can be established that the recognition of hyperconvoluted cells in small numbers is a reproducible finding and occurs only in dermatopathic lymphadenopathy associated with MF and not in dermatopathic lymphadenopathy associated with other dermatoses, further investigation should be directed toward determining the biologic significance of quantitating

LN-0: No atypical lymphocytes (AL) with cerebriform or convoluted nuclei recognized

LN-1: Occasional and isolated AL identified (not arranged in clusters)

LN-2: Many AL, occurring singly or in 3–6 cell clusters

LN-3: AL arranged in aggregates (nodal architecture essentially preserved)

LN-4: Partial or complete replacement of nodal architecture by AL or frankly neoplastic cells

FIGURE 1.—Classification of patterns of lymph node involvement in cutaneous T cell lymphomas (proposed by M. Matthews and A. Gazdar). (Note: Dermatopathic lymphadenitis is a prominent feature of all lymph nodes except where architecture is effaced)

hyperconvoluted cells in the lymph nodes of patients with MF. The question that needs to be answered is whether the presence of such cells in small numbers and not in cohesive clusters or masses represents histologic evidence of "lymph node involvement" and thus would disqualify a patient from being considered for a treatment protocol employing topical mechlorethamine or electron-beam irradiation without systemic chemotherapy.

Blood

In patients with elevated lymphocyte counts, peripheral blood involvement by malignant cutaneous T cell lymphoma cells is usually easily recognized by conventional Wright-Giemsa-stained peripheral blood smears. Although the mixed cell variant is more striking, the small cell variant is also readily recognized by the highly grooved chromatin of the nucleus in well-stained preparations. Determination of the T cell nature of the lymphocytosis serves to confirm the morphologic suspicion of blood involvement. Detection and quantitation of peripheral involvement in the patient with a low lymphocyte level is a more difficult matter. In this situation there was general agreement that the best method for examining the peripheral blood remains uncertain. While careful morphologic evaluation by light-microscopic techniques of a large number of lymphocytes (eg, 50–200 lymphocytes), carefully prepared either in peripheral blood smears or concentrated preparations such as buffy-coat or isolated lymphocyte preparations, was considered helpful by some workers, others felt that accurate assessment could only be made at the electron-microscope level or possibly with 1-μ sections at the light-microscopic level. It was recommended that pilot studies be done at at least two centers which have some experience in this matter before specific recommendations are made. These studies should include comparisons derived from studies of blood smears and buffy-coat preparations. For example, one study should involve the preparation of 1-μ sections from three blocks of purified lymphocytes with the counting of a minimum of 500 cells for each of the three blocks. The prognostic significance of detecting peripheral blood involvement by any of these methods in patients with low or normal numbers of peripheral blood lymphocytes remains to be determined.

Funding

It was strongly suggested that active discussions be carried out with appropriate officials of the NCI to discern the best method for applying for and obtaining secure long-term funding for a central pathology registry and panel activities.

APPENDIX

Glossary of Histopathologic Terms

EPIDERMIS

Hyperkeratosis—increased thickness of stratum corneum. May or may not have increased thickness of granular layer. Degree may be indicated if unusual.

Parakeratosis—retention of nuclei in the stratum corneum. Granular layer is usually absent. Degree or proportion to non-parakeratotic epidermis may be indicated.

Acanthosis—increased thickness of epidermal malpighian layer.

Psoriasiform—elongation of the rete ridges, often narrow above and broad and club-shaped at apices. Suprapapillary portion of epidermis may be of normal thickness or thinner or thicker than normal.

Lichen planus-like—rete ridges in an irregular "sawtooth" configuration with pointed apices. Epidermis may appear arched between pointed rete ridges.

Atrophy—epidermis reduced in thickness. Rete ridges may show complete effacement.

Poikilodermatous—epidermis uniformly thin with effacement of the rete ridges. Basal layer shows variable liquefaction degeneration (*see* below). Upper dermis has associated inflammatory infiltrate often in bandlike configuration.

Ulceration—loss of total epidermal thickness over variable area, usually associated upper dermal damage and an associated dermal inflammatory response.

Spongiosis—extracellular epidermal edema. Cellular attachments ("prickles") are prominent, adjacent cell borders are separated. When severe, vesiculation or intra-epidermal bulla formation occurs.

Intracellular edema—edema within squamous cells which appear pale and swollen. When severe, multilocular bulla formation occurs.

Liquefaction degeneration of basal layer—basal cells selectively affected. Varies from simple edema and vacuolization of basal cells to total degeneration of basal cell layer. May be associated with loss of pigment into the upper dermis (pigment incontinence) or may be associated with diffuse exocytosis.

Exocytosis—migration of inflammatory cells from dermis into epidermis. Migration of lymphoma cells is also included in this category.

Diffuse epidermal infiltration—major extent of epidermis infiltrated but no cell grouping present. Degree may be sparse to massive. May be associated with liquefaction degeneration of the basal cell layer.

Microabscess—small accumulations of cells in epidermis. Cells often appear to lie within a small cavity. Should be distinguished from vesiculation with its associated spongiosis. May occur in surface or adnexal epithelium.

Pautrier—small accumulations of atypical mononuclear cells in the epidermis. Cells are usually similar to those of dermal infiltrate and usually do not include inflammatory cells. Cells lie at any level of malpighian layer, but lower ones must be distinguished from sections of dermal papillae.

Inflammatory—similar to Pautrier microabscess but contains inflammatory cells in addition to any mononuclear cells.

CELLULAR INFILTRATE

Monomorphous—all cells of infiltrate from same cell line, ie, lymphocytes, histiocytes. Any consistent appearance of a second cell type in representative areas classifies infiltrate as polymorphous.

Types of cells

Mature lymphocyte—small round cell with deeply staining nucleus with clumped chromatin pattern. Cytoplasm is indistinct or forms a narrow rim around the nucleus.

Immature lymphocyte—larger round cell with large round to slightly indented nucleus. Nucleus is larger and paler than nucleus of mature lymphocyte; has distinct, relatively evenly distributed chromatin pattern. May appear vesicular. Narrow rim of slightly basophilic cytoplasm surrounds nucleus.

Reticulum cell—large mononuclear cell which, on morphologic features alone, cannot be classified with assurance as either lymphocytic or histiocytic. Nucleus is oval, indented reniform, with distinct basophilic nuclear membrane. Contains chromatin granules or clumps; nucleoli may be prominent. Cytoplasm is usually abundant, eosinophilic, and may have irregular configuration with ameboid appearance.

Fibroblast—nuclei usually spindle-shaped, pale-staining, with a fine nuclear membrane. May appear vesicular. Cytoplasm is not distinct. Cells lie in parallel orientation with collagen fibers. Less mature cells have larger, more plump, paler-staining nuclei.

Epithelioid cell—large, usually oval, pale-staining nucleus with vesicular appearance. Has abundant, slightly eosinophilic cytoplasm. Cells are usually organized in groups without identifiable cell borders.

Giant cell—large multinucleated cell.

Foreign body giant cell—nuclei clumped or in irregular arrangement.

Langhan's giant cell—nuclei at periphery of cell in horse-shoe arrangement.

Touton giant cell—central nonfoamy cytoplasm surrounded by a ring of peripheral foamy cytoplasm.

Anaplastic giant cell—highly abnormal-appearing neoplastic cell with marked nuclear pleomorphism. Appearance not sufficiently specific to be classified as Sternberg-Reed-like cell.

Cell resembling Sternberg-Reed cell—resembling or indistinguishable from Sternberg-Reed cell of Hodgkin's disease. Cell is large (12–40 μ in diameter) with large prominent nuclei. Double bean-shaped nucleus with mirror-image appearance is characteristic. May have perinucleolar halo. Nuclear chromatin is coarse, tends to concentrate near distinct nuclear membrane. Each nucleus usually has large homogeneous-appearing nucleolus, usually eosinophilic.

Hyperconvoluted cell—an atypical lymphocyte which may be smaller or larger than a histiocyte (10–30 μ). The large nucleus may be hyperchromatic or pale-staining. The nuclear membrane has a convoluted, indented, or cerebriform appearance. Cytoplasm is usually scanty and indistinct. This is not a phagocytic cell.

Mycosis cell—a variant of the hyperconvoluted cell in which the large, irregular, deeply staining (hyperchromatic) nucleus is the primary feature and may obscure the hyperconvolutions of the nuclear membrane and other nuclear detail. Larger than a histiocyte. Cytoplasm is scanty and not distinct. This is not a phagocytic cell.

DERMIS

Grenz zone—area of uninvolved connective tissue separating epidermis from underlying dermal infiltrate. Often in the form of a band of variable thickness; may be irregular.

Diffuse infiltrate—infiltrate widespread without segregation into patches or masses, borders not well-defined. Density varies from minimal to marked.

Patchy infiltrate—infiltrate segregated into patches or masses. Usually sharply marginated although may have groups of cells extending outward from masses.

Bandlike subepidermal infiltrate—confined to upper dermis in narrow to broad band running parallel to surface epidermis. May or may not be associated with grenz zone.

Dermal connective tissue

Collagenized (sclerotic, hypocellular)—normal fibrillar pattern indistinct, collagen appears denser than normal, usually more eosinophilic than normal; fewer fibroblastic nuclei. Orientation of collagen fibers may be disturbed.

Young collagen, fibroblastic proliferation—collagen may show pallor, relative basophilia. Increased number of fibroblasts, having plump nuclei, lie in orderly arrangement between collagen fibers. Increased content of hyaluronic acid (demonstrated by colloidal iron, alcian blue, or similar stains).

Increased reticulum fibers—demonstrated with special stains, accompanies fibroblastic response.

Mucin deposition—suggested by pallor of collagen, separation of collagen fibers and deposition of stringy or granular amorphous basophilic material in interstices. Demonstrated with special stains.

Infiltrate pushing aside or compressing connective tissue—usually associated with patchy cellular infiltrates. Connective tissue appears to react to confine infiltrate.

Cellular infiltration between collagen fibers—usually associated with diffuse cellular infiltrates. Connective tissue appears to be invaded by infiltrate. Single columns of cells may extend between collagen fibers. Connective tissue shows no evidence of reaction to cellular process.

Pilosebaceous follicles

Mucin deposition—seen in sebaceous gland and/or outer root sheath of hair follicle. Foci of intercellular edema, disruption of cells, deposition of granular or stringy basophilic material in resulting cystic spaces. Demonstrated by colloidal iron, alcian blue, or similar stains. Picture of alopecia mucinosa.

Pathologic Diagnostic Definitions

Chronic dermatitis—The epidermis usually shows variable acanthosis. There may be occasional foci of spongiosis and exocytosis of normal-appearing lymphocytes. The upper dermis shows a patchy, usually predominantly perivascular infiltrate of normal-appearing lymphocytes and few numbers of histiocytes. Eosinophils and plasma cells may be present. The blood vessels may show some thickening of walls.

Atypical cellular infiltrate with features suggesting MF—The skin shows a largely benign-appearing infiltrate but has exocytosis which may be out of proportion to the degree of spongiosis. This may suggest Pautrier microabscesses. The dermal infiltrate has some atypical-appearing lymphocytes but not in sufficient numbers or variability to allow a definite diagnosis of MF.

Lichenoid dermatitis—The epidermis varies in thickness but usually shows reduced prominence of the rete ridge pattern except for areas where there may be a suggestion of "saw-toothing." The basal cells may show edema, and there may be associated lower dermal spongiosis. Focal or more diffuse exocytosis into the lower epidermis may occur, although the migrating cells appear normal. The upper dermis shows a patchy to bandlike infiltrate of normal-appearing lymphocytes in close association with the epidermis. Small numbers of other inflammatory cells may be present.

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Report of the Committee on Staging and Classification of Cutaneous T-Cell Lymphomas

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There are two purposes for classifying diseases into stages. The first purpose is to stratify cases according to prognosis so that defined therapy can be given to homogeneous subsets. The second purpose is to facilitate communication between investigators. Two examples that have served these purposes are the Rye and Ann Arbor staging classifications for Hodgkin's disease (1). Several staging classifications have been proposed for the cutaneous T-cell lymphomas (CTCL). However, comparisons between these schemes are difficult (2–4) because differing features have been used to segregate groups. We believe, as do others (5), that there is a critical need for a uniform staging system in CTCL.

In addition to uniform classification definitions, certain minimum staging procedures should be performed in patients with CTCL. Such procedures would assist in the classification as well as in the determination of the extent of disease before and after therapy. This report will recommend procedures to be performed in all patients to provide such information.

Previous studies showed that extent of disease in the skin, lymph nodes, and visceral organs has prognostic importance (5–8). More recently, it was recognized that the number of circulating atypical lymphocytes may also have prognostic significance.[4] Therefore, the staging system must be able to describe multiple parameters. The relative importance of each of these parameters is not yet clear so the staging system must be flexible enough to group some of these factors until their value is known.

The TNM classification system, recommended for some other tumors by the American Joint Committee on Cancer Staging, does have the potential for accurate and flexible classification. The major advantage of the TNM system is that it allows for detailed recording of characteristics that describe each patient. Modifications to the TNM system for mycosis fungoides (MF) have been proposed by the Mycosis Fungoides Cooperative Group (9) which has now had 4 years of experience with the system. Table 1 shows further modifications of that scheme and the combining of certain clinical and pathologic features.

The T represents the skin stage of the patient. T_0 lesions are clinically and/or histopathologically suspicious of a CTCL. However, the skin biopsies are not unequivocally diagnostic. Repeat skin biopsies at intervals are recommended for these patients if the lesions persist or progress, since an unknown fraction of these patients will develop a CTCL. For T_1–T_4 lesions, skin biopsies are diagnostic of a CTCL. T_1 lesions represent limited plaques, papules, or eczematous patches that cover < 10% of the body skin surface. For convenience, the palmar surface of the hand represents about 1% of the skin surface. T_2 lesions represent generalized plaques, papules, or erythematous patches covering ≥ 10% of the skin surface. T_3 lesions represent the presence of one or more skin tumors. T_4 lesions represent generalized erythroderma. When more than one T lesion exists, the highest is used for staging although both are recorded. For example, a patient with generalized plaques and a tumor would be $T_{3(2)}$, while a patient with generalized erythroderma and a tumor would be $T_{4(3)}$. Other clinical features associated with the

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TABLE 1.—TNM classification of CTCL

Classification	Description
T: skin*	
T_0	Clinically and/or histopathologically suspicious lesions
T_1	Limited plaques, papules, or eczematous patches covering < 10% of the skin surface
T_2	Generalized plaques, papules, or erythematous patches covering ≥ 10% of the skin surface
T_3	Tumors (≥ 1)
T_4	Generalized erythroderma
N: lymph nodes†	
N_0	No clinically abnormal peripheral lymph nodes, pathology negative for CTCL
N_1	Clinically abnormal peripheral lymph nodes, pathology negative for CTCL
N_2	No clinically abnormal peripheral lymph nodes, pathology positive for CTCL
N_3	Clinically abnormal peripheral lymph nodes, pathology positive for CTCL
B: peripheral blood	
B_0	Atypical circulating cells not present (< 5%)
B_1	Atypical circulating cells present (> 5%); record total wbc and total lymphocyte counts and No. of atypical cells/100 lymphocytes
M: visceral organs	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)

*Pathology of T_{1-4} is diagnostic of a CTCL. When > 1 T exists, both are recorded and the highest is used for staging, eg, $T_{4(3)}$.

†Record No. of sites of abnormal nodes, eg, cervical (left + right), axillary (left + right), groin (left + right), epitrochlear, submandibular/submaxillary.

skin lesions such as ulceration, poikiloderma, exfoliation, etc, may have prognostic significance and their presence should be recorded until their relative importance is known.

The N represents the peripheral lymph nodes. The lymph nodes are scored N_0–N_3 depending on physical examination and histologic examination of biopsied nodes. N_0 indicates that there are no clinically enlarged nodes. Blind lymph node biopsies in these N_0 patients are negative for CTCL. N_1 indicates that clinically enlarged nodes are present but that lymph node biopsy is not diagnostic of CTCL. N_2 indicates that there are no clinically abnormal nodes but blind lymph node biopsy is positive for CTCL. N_3 indicates that clinically abnormal nodes are present and are histologically positive for CTCL on biopsy. The number and sites of abnormal nodes should be recorded. Investigations to correlate the degree of infiltration as well as the findings of sinus histiocytosis, dermatopathic lymphadenitis, and other pathologic subsets should be undertaken.

The B represents the peripheral blood involvement. B_0 indicates that peripheral blood is not involved with lymphoma. This means that < 5% of all lymphocytes exhibit an atypical convoluted appearance by light microscopy. Since patients may be lymphopenic, the absolute lymphocyte count should be recorded and at least 100 and preferably 500 lymphocytes should be scored. B_1 indicates that > 5% of the circulating lymphocytes are atypical and convoluted. The percentage of atypical cells should be recorded in all cases.

M_0 and M_1 represent negative and positive visceral organ involvement respectively. Visceral involvement must be documented pathologically and the specific organ(s) recorded.

Staging Classification

The clinical staging classification (table 2) is based on the T, N, and M nomenclature. Since it is not clear whether peripheral blood is an independent prognostic variable, unrelated to node and/or visceral involvement, it has not been incorporated into the staging classification. However, it should be recorded for each patient so that its prognostic value can later be determined. Stage I patients are those whose lesions are confined to the skin without clinical adenopathy. Stage IA patients are those with limited (< 10%) plaque disease ($T_1N_0M_0$) and stage IB patients are those with generalized (≥ 10%) plaque disease ($T_2N_0M_0$). Stage II patients comprise several subsets of patients. Stage IIA patients are those with plaques and adenopathy ($T_{1,2}N_1M_0$) and stage IIB patients are those with skin tumors with or without clinical adenopathy

TABLE 2.—Staging classification of CTCL

Stage	Classification		
	T	N	M
IA	1	0	0
IB	2	0	0
IIA	1–2	1	0
IIB	3	0,1	0
III	4	0,1	0
IVA	1–4	2,3	0
IVB	1–4	0–3	1

($T_3N_0M_0$). By definition, lymph node biopsies are negative for CTCL in these patients. Stage III patients have generalized erythroderma with or without adenopathy ($T_4N_{0,1}M_0$). By definition, lymph node biopsies are not diagnostic for CTCL in these patients. Stage IV also comprises several groups of patients with biopsy-documented pathologic involvement of lymph nodes (stage IVA) or visceral organs (stage IVB). Patients may have any skin stage (T_1–T_4) and may or may not have adenopathy (N_0–N_3). In each patient, the exact T, N, and M should be recorded since this stage may include patients with Sézary syndrome, tumors with visceral involvement, or other permutations.

Staging Procedures

The staging procedures required for all patients are as follows:

(*a*) Complete history and physical examination.
(*b*) Whole-body mapping of lesions.
(*c*) Cbc, differential, platelet, and absolute lymphocyte counts (100–500 lymphocytes), and record of atypical convoluted lymphocytes.
(*d*) Serum chemistries, liver function tests, renal function tests, uric acid, calcium, and phosphorus.
(*e*) Chest roentgenogram.
(*f*) Skin biopsy and lymph node biopsy (palpable node from draining area using cervical before axillary before groin; if not palpable, "blind" biopsy is to be obtained).
(*g*) Liver and bone marrow biopsies only from stages II, III, and IV.
(*h*) Evaluation of other organs when involvement is suggested by history or physical examination.

Note: Lymphangiogram is suggested for patients who receive systemic therapy as a means to follow remissions but is not done routinely; multiple liver biopsies and peritoneoscopy are preferred to single-needle biopsy.

These procedures should be performed prior to starting therapy. Whole-body mapping of lesions as demonstrated in table 1 is preferable to whole-body photographs. Photographs vary greatly in quality, are expensive, and may not reflect infiltration. Lymph node biopsies should be performed in all patients including those without clinical adenopathy. These biopsies should be obtained from nodal areas draining skin involved with CTCL. When multiple areas of skin are involved, the following preference should be used for determining biopsy sites: (*a*) cervical, (*b*) axillary, and (*c*) inguinal and/or femoral. Liver and bone marrow biopsies should be obtained from all patients with generalized erythroderma or skin tumors and from patients with plaques who have clinical adenopathy (ie, stage II, III, and IV patients). Evaluation of other organs should be performed when involvement is suggested by history or physical examination. For example, a patient with bone pain should have a bone scan, a roentgenogram of the area, and a biopsy if the scan or roentgenogram is positive. Since lymphangiograms are rarely positive in patients without clinical adenopathy, their use is not a requirement. However, lymphangiography is probably useful in following response to systemic therapy. Multiple liver biopsies obtained at peritoneoscopy are more sensitive than a single percutaneous biopsy in CTCL as well as in other lymphomas and are recommended.

Re-Staging Procedures

The recommended re-staging procedures are as follows:

(*a*) Complete history and physical examination.
(*b*) Whole-body mapping of lesions.
(*c*) Cbc, differential, platelet, and absolute lymphocyte counts (100–500 lymphocytes), and record of atypical convoluted lymphocytes.
(*d*) Serum chemistries, liver function tests, renal function tests, uric acid, calcium, and phosphorus.
(*e*) Repeat skin biopsies.
(*f*) Repeat tests if initially abnormal:
1. Chest roentgenogram.
2. Lymph node biopsy.
3. Liver biopsy.
4. Bone marrow biopsy.

(*g*) Re-evaluation of other initially abnormal findings.

Note: Patients are in complete remission if there is no clinical *and* histologic evidence of disease including results of skin biopsy, peripheral blood evaluation, and repeated initially abnormal parameters.

These procedures should be performed to document remissions and/or whenever there has been progression of disease and a new therapy is contemplated. It should be stressed that a complete remission means histologic as well as clinical disappearance of tumor. Therefore, all tissues initially involved with CTCL should be re-biopsied at the time clinical complete remission is achieved. An exception to this principle is that lymph node biopsy need not be repeated if there are no palpable lymph nodes at the time of re-staging.

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Report of the Committee on Therapy for Mycosis Fungoides and Sézary Syndrome [1]

John D. Minna, [2,*] Henry H. Roenigk, Jr, [3] and Eli Glatstein [4]

This committee restricted its discussion to therapy for unequivocal, biopsy-proven mycosis fungoides (MF) and Sézary syndrome. The prognostic effect of stage of disease, lymph node involvement, and clinical histopathologic correlations was discussed by the committees on staging and pathology (1,2). The therapy committee concluded that many studies were difficult to interpret and urged that future reports of therapy for MF and Sézary syndrome (cutaneous T-cell lymphomas [CTCL]) include the following:

1. Histologic criteria used for the diagnosis of CTCL in skin, lymph nodes, peripheral blood, and any other sites reported.

2. Presentation of all available clinical and histologic data used in staging patients irrespective of the staging system used.

3. Report of all prior treatment for each individual patient.

4. Report on criteria used for judging response. The panel urged the use of histologic restaging at the time of maximum response and suggested that the models of restaging used in other malignant lymphomas are relevant to MF and Sézary syndrome. The criteria used to score the response, the time from start of treatment to maximum response, the presence or absence of relapse, the time to relapse, the actuarial disease-free survival, and the overall survival should be presented.

5. Report of all deaths including the cause and the data concerning the presence or absence of CTCL in necropsy specimens.

6. Report of the exact treatment given to each patient including dose, fractionation, timing, schedule, electron dosimetry, and criteria used for any therapy modification. This applies to radiotherapy, PUVA (8-methoxypsoralen plus ultraviolet light) therapy, all forms of topical therapy, and systemic chemotherapy.

7. Report on treatment-related acute and chronic toxic effects to skin, bone marrow, and other organs, infectious complications, and treatment-related morbidity and death (including report of histologically documented second primary neoplasms).

8. The natural history of MF may be long and notoriously subtle; the panel urged restraint from euphoric claims without prolonged followup (a minimum of 3–5 years) before interpreting the effectiveness of treatment. The available data suggest that the induction of a complete response (complete clinical and histologic disappearance of disease) may be of great importance, not only to quality of life but also probably to survival (3–5). Thus, the committee urged that reports, studies, and retrospective analyses be presented in a manner designed to support or refute this notion. The committee recognized and discussed that there are two different approaches to CTCL therapy: early aggressive therapy with "curative" intent and long-term conservative therapy with essentially palliative intent. The committee agreed that, at present, there are no data from any controlled trials to support one approach over the other (see, for example, the differences in opinion expressed in the therapy papers in this issue).

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Radiotherapy

The use of radiation therapy in the management of CTCL is reviewed in this issue by Hoppe et al (4). The committee discussion dealt almost exclusively with electron-beam (EB) therapy. The consensus was as follows:

Any of the several multiple-field techniques for delivering EB therapy are acceptable including four-, six-, or rotational-field techniques; the choice of technique depends on the equipment and expertise available at each institution (3–13).

The dosimetry, the photon contamination of the EB therapy, the EB depth-dose distribution, and the dosimetric confirmation of homogeneity of depth-dose for the specific technique used should be included in any EB therapy report. Radiation physics monitoring by a central source is desirable for evaluation and comparison of individual EBs (4).

Increased EB dose appears to be correlated with increased response rate, complete response rate, freedom from relapse, and survival for at least some cohorts. Although these data come from retrospective series, the relapse rate of patients treated with lower doses of EB therapy at several centers appears to confirm these observations (3–13).

The radiotherapists felt that a total dose of 3600 rads of EB therapy to a depth of 8–10 mm (in 8–12 weeks) appears to be the tolerable upper limit, and various fractionation schemes including one, two, and four times per week are all acceptable. In practice, the EB dose is limited by skin tolerance (3–5), with acute radiation dermatitis being a well-defined clinical entity. Patients with total-skin erythema or fair skin appear to be extremely sensitive (4), and great care must be taken with the EB dose to prevent severe skin toxicity. The fractionation used frequently depends on consideration of expense, logistics, and individual patient tolerance. The committee recommended that all reports include information on whether EB therapy was given to skin tolerance.

Re-treatment with EB therapy depends on the radiotherapist's individual clinical judgment of skin condition. The Stanford University group reports giving two full courses (total, 6000 rads) to carefully selected patients (reported anecdotally by R. Hoppe and Z. Y. Fuks).

EB therapy can be given per primam or after topical or systemic chemotherapy. However, telangiectasia, chronic radiodermatitis, and skin atrophy are more frequent in patients treated with EB therapy after lengthy courses of topical chemotherapy (4). Conversely, patients appear to tolerate well topical mechlorethamine, systemic chemotherapy, or PUVA after EB therapy (5,14). However, the committee members mentioned anecdotal cases of severe cutaneous toxic effects when systemic chemotherapy is given after EB therapy. The agent has not been identified but the committee suggested methotrexate as one possible candidate.

The importance of vertical staging (depth of skin involvement) before EB therapy was emphasized with the depth of plaque or tumor invasion identified as an important variable (15). However, there are no published data relating this to results with EB or PUVA therapy and these are required.

The Stanford University Division of Radiotherapy group reported that for limited plaque-disease patients with or without palpable nodes, > 40% are long-term (9 years) disease-free survivors whose treatment has been discontinued and who are potentially cured (4,5). In addition, this group reports that 96% of limited plaque-disease patients achieve an initial complete clinical remission with EB therapy alone while 84% of all patients they treat achieve a complete remission (4,5). These results need to be confirmed by other radiotherapy centers and compared to other modalities of treatment, but at present they represent the best results reported. The results of several large series of patients receiving EB therapy with the emphasis on patients with early-stage disease are shown in table 1.

When nodes are involved either clinically or histologically, treatment was felt to be essential because the prognosis is significantly worse than without palpable or involved nodes (5,7). The Stanford University group has treated three such patients with EB therapy and concomitant total-nodal radiotherapy; they report no unexpected toxic effects (4). Their current trial of patients with dermatopathic lymphadenopathy involves randomizing patients to treatment with either EB therapy followed by topical mechlorethamine or EB therapy with concurrent total-nodal irradiation followed by topical mechlorethamine.

Total-body irradiation of approximately 150 rads has been given to three patients at Stanford University and some of these patients have had an objective response (reported anecdotally at this meeting). Some of the committee radiotherapists feel this modality might have a potential role as part of initial therapy.

Half-body radiotherapy was not discussed (4).

It was emphasized that EB treatment of the entire skin is technically, dosimetrically, and physically difficult, and should not be embarked upon without prior experience with the techniques or without excellent physics support.

TABLE 1.—Results of EB treatment of CTCL and comparison to topical mechlorethamine treatment with emphasis on early-stage disease

Center (ref Nos.)	No. of patients treated	% of patients with—*				Median duration (mos) of—	
		Limited disease	Adenopathy	CR	Continuous CR	Remission	Survival
EB therapy							
Stanford University (4,5), 1966–1978	140	18	58	84	26	16†	108+
Limited plaque‡	20	100	0	100	65	48+	108+
Memorial Sloan-Kettering Cancer Center (7), 1971–1978	81	6	91§	100	12	9	NR
Limited plaque	10	100	0	100	100	45	44+
Mt. Zion (11), 1971–1976	39	13	39	41	18	12	12+
Limited plaque	5	100	NR	100	60	37+	37+
Lahey Clinic (12), 1964–1973	31¶	NR	NR	31	7¶	21	36
Total EB therapy							
All patients	291	13 (35 of 260 patients)	65 (170 of 260 patients)	77	19	9–21	12+–108+
Limited plaque	35	100	0	100	74	37+–48+	37+–108+
Topical mechlorethamine							
Temple University (16–18), 1968–1978	243	47	37	64	35	18+**	34+
Limited plaque	79	100	0	80	53	28+	37+

*CR = complete clinical regression of disease; NR = not reported.

†Estimated from fig 3 of Hoppe et al (5).

‡Some patients in the limited-plaque, no-adenopathy group were randomized to receive topical mechlorethamine.

§Data are given for total group of only 109 patients and % adenopathy is taken from this.

¶Only patients receiving ≥ 2000 rads of EB therapy are included. The continuous CR data are taken from the total series and it is estimated that 2 of 31 patients (7%) receiving ≥ 2000 rads are in continuous CR. This is the most conservative estimate.

**Remission while receiving maintenance topical mechlorethamine therapy.

Topical Chemotherapy

The consensus of the committee was as follows:

In addition to EB therapy, topical application of mechlorethamine is a proven regimen for control of cutaneous disease in CTCL (16–19). Vonderheid et al (18) summarized the Temple University experience, with 155 of 243 patients (all stages) achieving a complete clinical remission while receiving active treatment. The exact mechanism of action of topical mechlorethamine is not known and topical delayed hypersensitivity induction (possibly one mechanism of topical mechlorethamine action) is another form of topical therapy that the committee felt should be explored (17,18).

Long-term disease-free survival of limited plaque disease after long-term topical mechlorethamine has been achieved, but this modality of treatment remains to be quantitatively compared to the results with EB therapy. Vonderheid et al (18) noted that in the Temple University experience there were 32 patients in complete remission for > 3 years, including 11 of 16 patients whose therapy was discontinued without relapse (18). In addition, patients with complete remissions for > 3 years can still relapse when topical mechlorethamine is discontinued. The Temple University group, after comparing their results to the Stanford University data, felt that, "Comparison of treatment results with those published on a large group of patients treated with total-skin electron-beam radiation therapy indicates that the chemotherapeutic approach to the treatment of MF is equally effective in promoting survival" (18).

The committee, which represented the different disciplines of topical chemotherapy (eg, E. Van Scott), PUVA therapy (eg, H. H. Roenigk, Jr), and EB therapy (eg, R. Hoppe and Z. Y. Fuks), is interested in pursuing trials of multimodality combinations of topical therapy (ie, testing various combinations of topical mechlorethamine, EB, and PUVA), even in patients who have achieved complete clinical remissions. Note is made of the ongoing Stanford University trial where, after receiving EB radiotherapy, the patients are randomized to receive or not to receive topical mechlorethamine therapy (5,14). Van Scott recommended considering treatment with all topical modalities in an intensive sequential manner. No data are yet available from randomized trials to distinguish the effect on pa-

TABLE 2.—Summary of recent results with PUVA in the treatment of CTCL including MF and Sézary syndrome (SS)

Author (ref No.)	Disease	No. of patients treated	No. of patients with— Clinical complete response	Long-term control/ total No. evaluated	Duration of control (mos)
Gilchrest (24)	MF	7	4	4/11	8–96
	SS	4	3		
Roenigk (25)*	MF	29	20	8/12	36+
	SS	7	2		
Hodge et al (28)	MF	6	4	NR†	NR
Thomsen (29)	MF	38	23	NR	NR
Totals	MF	80	51 (64%)		
	SS	11	5 (45%)		

*Includes data from the Cleveland Clinic, Northwestern University Clinic, and Mayo Clinic (Spigel and Muller).
†NR = not reported.

tient survival from multimodality therapy given initially versus such therapy given sequentially or at the time of relapse.

Topical corticosteroids (20) and natural sunlight with its ultraviolet components are effective modalities that were not discussed by the panel.

H. Zackheim, from the University of California Medical Center, reported on 37 patients with MF or Sézary syndrome treated with topical BCNU; 24 (65%) of these patients had "satisfactory control," including seven who had disease clearance after initial therapy and where disease remained clear without further treatment for at least 6 months. However, dermatitis was seen in all patients and was severe in 33%, while mild bone marrow suppression was seen in 30% of patients receiving total-skin BCNU. BCNU does not cross-react with mechlorethamine and can therefore be used in patients who are allergic to mustards (21,22).

Argyropoulos et al (23) reported on a double-blind multi-institutional study of chemotherapeutic agents applied topically to MF patients. Improvement was seen with cytosine arabinoside, dianhydrogalactitol, DTIC, guanazole, VM-26, hydroxyurea, thioTEPA, and methotrexate.

Methoxsalen Photochemotherapy

Gilchrest (24) and Roenigk (25) have summarized their results and those of others with PUVA in the 320–400-nm spectrum and in addition discussed the photobiology. The committee found that prolonged PUVA therapy was effective in achieving clinical control in all stages of skin disease, although skin tumors are often treated with supplemental therapy (24–29). Clinical clearing is correlated with histologic clearing of disease (25), and has frequently been seen in patients failing to respond to prior topical therapy with corticosteroids, mechlorethamine, and EB therapy (25,26). Table 2 summarizes the most recent data available.

The long-term side effects of PUVA therapy are not known. The committee noted that PUVA therapy is carcinogenic in some animal test models as well as having other biologic effects (cataracts) (24,25). The question of the degree of carcinogenicity of PUVA therapy remains to be resolved. For these reasons, PUVA therapy should still be considered experimental.

The available information indicates that PUVA must be given continuously for maintenance of clinical remission since many relapses have been seen when PUVA therapy is stopped (24,25). However, the PUVA therapists felt their experience suggests that a large fraction of patients are disease-free for periods of ≥ 3 years while they are maintained on PUVA therapy (24,25).

The committee noted that some groups begin giving PUVA therapy in early disease. Spittle (10) indicated that in England patients with early-plaque MF receive PUVA therapy first; if the patient fails to respond to PUVA therapy, then EB therapy is given. In more extensive-disease patients, EB therapy is given first followed by PUVA maintenance therapy (10). Again, the committee chairmen noted the absence of data from any prospective trial which would help determine whether "aggressive" curative attempts of treatment, eg, with EB therapy, are superior to "more conservative" initial treatment with PUVA therapy in terms of quality or quantity of survival.

TABLE 3.—Response to single-agent chemotherapy in CTCL

Agent	No. of patients treated	% of— Objective responses	% of— CRs*	Duration of response* (mos)	Ref Nos.†
Mechlorethamine	86	67	28 (13/46)	1–12+	30, 31
Cyclophosphamide	76	66	NR	3–14+	30
Chlorambucil	69	57	NR	NR	30
BCNU	14	50	NR	NR	30
Methotrexate	46	52	20 (6/30)	4–20	30
High-dose methotrexate + leucovorin rescue	11	100	64 (7/11)	6–30+ (CR)	32
Actinomycin D	13	46	NR	NR	30
Bleomycin	32	59	22 (7/32)	1–8+	29, 30, 33, 34
Adriamycin	13	62	23 (3/13)	3–10+	35
Vinblastine	14	50	NR	1–11	30
Vincristine	13	23	NR	NR	30
Procarbazine	6	33	NR	3	30
Corticosteroids	46	52	NR	0.5–24	30
VP-16-213	11	77	44 (4/9)	NR	29, 36

*Nos. in parentheses = No. of patients responding/total No. evaluated. NR = not reported. CR = complete clinical regression of disease.

†Ref 30 by Levi and Wiernik contains the original citations and summarizes much of the single-agent data.

Systemic Chemotherapy

A summary of the current response rate data to single-agent chemotherapy is shown in table 3. Most of the previous reports have been well-summarized by Levi and Wiernik (30). Spittle felt these reported response rates were much higher than her experience had shown. The committee urged publication of all single-agent response data to help determine the true response rates. Although not stated in many of these papers, most of these single agents had been given to patients after they had failed to respond to topical mechlorethamine, topical corticosteroids, or EB therapy, and thus probably represent non-cross-resistance with these other modalities. The response to single-agent chemotherapy after failure of PUVA therapy needs to be reported. Because of the importance of documenting this non-cross-resistance, the committee urged that all future reports indicate all prior systemic and topical therapy that the patients have received.

Single agents inducing documented complete clinical remissions include: systemic mechlorethamine, methotrexate, high-dose methotrexate with leucovorin rescue, bleomycin, Adriamycin, and VP-16-213 (table 3). Single-agent therapy appears to be associated with responses of short duration (table 3).

A summary of the current response rate data to combination chemotherapy is shown in table 4. The objective response rates are > 90% in some cases but as yet there is no clear evidence that the complete response rates are increased over those induced by single-agent therapy. In addition, there are only very limited data on the duration of responses achieved with combination chemotherapy.

The committee recognized the effective palliation achieved with combination chemotherapy in some patients. However, there are as yet no clear long-term examples of patients with advanced disease surviving free from relapse after either single-agent or combination chemotherapy given alone. This is also reflected in the lack of a plateau on the survival curves (39).

The committee noted that there are no data available on dose-response or dose-scheduling relationships with either single-agent or combination chemotherapy to determine the optimum therapy with any regimen. The number of patients treated with any one regimen is small and as yet there are no convincing data that any regimen is better than any other regimen. Although the survival curves of the COP + Bleo (cyclophosphamide, vincristine, prednisone, plus bleomycin) regimen appeared to be better than those of the CHOP (cyclophosphamide,

TABLE 4.—Response to combination chemotherapy in CTCL

Regimen*	No. of patients treated	No. of objective responses/ No. of patients treated	No. of CRs/No. of patients treated†	Duration of response† (mos)	Ref Nos.
MOPP	4	4/4	NR	NR	37
Bleomycin + methotrexate	10	9/10	1/10 (10%)	NR	29
CHOP/HOP-COP/OAP	12	12/12	5/12 (42%)	4.5–17 (CR) 1.9–13.5 (PR)	38, 39
COP + bleomycin	12	11/12	2/12 (17%)	4.5–12 (CR) 0–18 (PR)	38, 39
COP	4	3/4	1/4 (25%)	NR	40
Chlorambucil + prednisone	8 (Sézary syndrome)	5/8	NR	NR	41
Chlorambucil + prednisolone	5 (MF)	2/5	0/5	NR	29
Totals		43/53 (81%)	9/41 (22%)		

*MOPP = iv mechlorethamine, vincristine, prednisone, and procarbazine; CHOP = cyclophosphamide, Adriamycin, vincristine, and prednisone; HOP = Adriamycin, vincristine, and prednisone; COP = cyclophosphamide, vincristine, and prednisone; OAP = vincristine, cytosine arabinoside, and prednisone. *See* refs for the exact doses and schedules used.

†NR = not reported. CR = complete clinical regression. PR = objective clinical response that was not a CR.

Adriamycin, vincristine, and prednisone) or HOP (Adriamycin, vincristine, and prednisone) regimens, the CHOP/HOP group with inferior survival was treated from 1972 to 1974, while the longer-surviving COP + Bleo group was treated more recently, from 1974 to 1977 (39).

Combined Modality Topical Therapy and Systemic Chemotherapy

The committee recognized that in current clinical practice most patients with advanced diseases are treated at one time or another with EB therapy, topical mechlorethamine, topical corticosteroids, PUVA therapy, and single-agent or combination systemic chemotherapy, and have thus received multiple modalities of therapy usually determined by disease relapse and resistance to prior therapy. There were three reports at the workshop of combined modality EB therapy and systemic chemotherapy given as per primam treatment.

Griem, from the University of Chicago, reported on eight patients, all of whom had failed to respond to topical mechlorethamine and/or PUVA therapy, who were treated with 4000 rads (80% dose at a 2-cm depth) of EB therapy followed by eight cycles of MOPP (systemic mechlorethamine, vincristine, systemic prednisone, and procarbazine) or COPP (systemic cyclophosphamide, vincristine, systemic prednisone, and procarbazine) (42). Six of these patients had tumors and four had lymph node involvement. He noted an increase in bone marrow toxicity, a decrease in ability to perspire, and permanent alopecia. Kaplan-Meier survival curves showed a $> 90\%$ projected survival at 3 years and a 70% disease-free survival at 3 years. Recurrences were limited and treatable with EB or topical mechlorethamine therapy. Although not presented to the committee, Griem cited the previous experience of Moran who found that EB therapy combined with single-agent alkylating systemic chemotherapy in prior trials had not proved to be as effective as the results found by Griem.

Rivkin reported on the Southwestern Oncology Group (SWOG) early experience with a combined modality trial that involves the Seattle and Tucson groups. Patients classified as stage II by the SWOG with dermatopathic lymph node involvement receive 3000 rads of EB therapy followed by eight cycles of CHOP + Bleo. Patients are then randomized to receive photon radiotherapy to the largest lymph node sites or no further therapy. In five patients there were no relapses and two patients remain disease-free for 26+ and 28+ months. Patients classified as stage I by the SWOG (generalized plaque or limited plaque) with negative lymph

nodes are treated with 3000 rads of EB radiotherapy and are then randomized to receive or not to receive chemotherapy. All patients receiving EB therapy alone have relapsed, but two of three of those receiving chemotherapy are disease-free.

Minna reported on the early results of the National Cancer Institute-Veterans' Administration Medical Oncology Branch trial (43). Patients with disease limited to the skin were treated with 2400–3000 rads of EB radiotherapy with concurrent simultaneous iv mechlorethamine systemic chemotherapy; four of five patients remain in continuous complete remission for 3+ to 20+ months. Twenty-eight patients with Sézary syndrome or lymph node involvement have been treated with EB therapy and simultaneous combination chemotherapy (vinblastine, Adriamycin, and bleomycin alternating with cycles of cyclophosphamide, methotrexate, and prednisone), and eight patients are in continuous complete remission for 20–27+ months. At 2 years the actuarial survival rate is 80%.

The committee urged that any anecdotal reports of patients treated with combined modality therapy be reported, since various participants knew of such patients with long-term survival.

The committee felt the results with combined modality therapy, particularly in patients with more advanced stages, were impressive, but that this method of treatment had to be compared in randomized trials to more conservative treatment (with topical therapy) in comparably staged patients to prove any overall survival benefit.

Other Therapies

Other therapies, such as the use of anti-thymocyte globulin (44,45) for relapsing patients or leukapheresis for patients with Sézary syndrome (46), should be considered highly experimental and the benefits need to be documented in further phase II trials.

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ANNOUNCEMENTS

Postgraduate Course on "Strategies of Care for the Cancer Patient"

Monterey, California, July 13–14, 1979

A postgraduate course on "Strategies of Care for the Cancer Patient" will be held July 13–14, 1979, at the Del Monte Hyatt House in Monterey, California. The program chairmen are David S. Gullion, MD, and George C. Knovick, MD. This program is presented by the Continuing Medical Education Advisory Council of the Central Coast Area Health Education Center and by Extended Programs in Medical Education of the University of California School of Medicine in San Francisco. The course is co-sponsored by the American Cancer Society (Fresno County and Monterey-San Benito County Units) and by the Northern California Cancer Program. The cooperation of the Monterey County Medical Society is also gratefully acknowledged.

The objective of this program is to assure the primary care physician's involvement as the keystone member of the treatment team for the cancer patient. The development of treatment strategies for both the clinical and psychosocial support of the cancer patient necessitates informed cooperation between the oncologist and the primary care physician. The continuum of care from risk determination through detection, treatment, and followup is an interdisciplinary effort that involves the primary care physician at every stage if the patient's treatment is to be "wholly successful."

As an organization accredited for continuing medical education, Extended Programs in Medical Education of the University of California School of Medicine at San Francisco (a division of Continuing Education in Health Sciences) designates this continuing medical education offering as meeting the criteria for 11.5 hours in Category I of the Physicians Recognition Award of the American Medical Association and the Certification Program of the California Medical Association.

The registration fee is $150.00 for physicians (includes continental breakfast and lunch) and $95.00 for interns, residents, and fellows, with letter of verification, on a space-available basis. *All registrations must be made in advance since attendance will be limited to 140 persons. Minimum attendance will be 100.* A service fee of $20.00 will be charged for refunds requested 1 week prior to the course; no refunds will be made after that date (to apply for refund, please return the registration receipt). *For further information and an enrollment form contact:* Extended Programs in Medical Education, University of California, 1308 3rd Ave, San Francisco, Calif 94143.

American Board of Internal Medicine Examinations

The next examinations in Hematology, Infectious Disease, Nephrology, Pulmonary Disease, and Rheumatology will be on June 17, 1980. Registration for these subspecialty examinations will begin August 1, 1979, and will continue through November 1, 1979. For those who began their residency training in internal medicine before June 1, 1970, and who have < 2 years of acceptable subspecialty training this will be the last opportunity for admission to a subspecialty examination. *Applications may be obtained from:* The American Board of Internal Medicine, University City Science Center, 3624 Market St, Philadelphia, Pa 19104 (telephone: 215-243-1500).

The American Board of Internal Medicine has announced a significant change in policy regarding its training requirements. This change will affect physicians desiring admission to a subspecialty examination who began their residency training in *internal medicine* before June 1, 1970. At present, these physicians are considered to have met the training requirements for admission to a subspecialty examination after completing 1 year of acceptable training in the subspecialty. If once informed of admission to a subspecialty examination, these physicians *will continue* to be considered to have fulfilled the Board's training requirements in that subspecialty. Beginning with the subspecialty examination offered in 1981, however, *all physicians* not previously admitted to an examination will be required to meet the same training requirements which apply to physicians beginning their

residency training after June 1, 1970. These requirements currently involve 2 full years of acceptable training in the subspecialty. A complete description of the Board's policies and procedures may be obtained by directing a written request to the American Board of Internal Medicine (above address).

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